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Calcium

BACKGROUND INFORMATION

Overview

Calcium accounts for 1 to 2 percent of adult human body weight. Over 99 percent of total body calcium is found in teeth and bones. The remainder is present in blood, extracellular fluid, muscle, and other tissues, where it plays a role in mediating vascular contraction and vasodilation, muscle contraction, nerve transmission, and glandular secretion.

In bone, calcium exists primarily in the form of hydroxyapatite (Ca_{10} $(PO_4)_6$ $(OH)_2$), and bone mineral is almost 40 percent of the weight of bone. Bone is a dynamic tissue that is constantly undergoing osteoclastic bone resorption and osteoblastic bone formation. Bone formation exceeds resorption in growing children, is balanced with resorption in healthy adults, and lags behind resorption after menopause and with aging in men and women. Each year, a portion of the skeleton is remodeled (reabsorbed and replaced by new bone). The rate of cortical (or compact) bone remodeling can be as high as 50 percent per year in young children and is about 5 percent per year in adults (Parfitt, 1988). Trabecular (or cancellous) bone remodeling is about five-fold higher than cortical remodeling in adults. The skeleton has an obvious structural role and it also serves as a reservoir for calcium.

Physiology of Absorption, Metabolism, and Excretion

Calcium is absorbed by active transport and passive diffusion across the intestinal mucosa. Active transport of calcium into enterocytes and out on the serosal side is dependent on the action of 1,25-dihydroxyvitamin D ($1,25(OH)_2D$), the active form of vitamin D, and its intestinal receptors. This mechanism accounts for most of the absorption of calcium at low and moderate intake levels. Passive diffusion involves the movement of calcium between mucosal cells and is dependent on the luminal:serosal calcium concentration gradient. Passive diffusion becomes more important at high calcium intakes (Ireland and Fordtran, 1973).

It has long been recognized that fractional calcium absorption varies inversely with dietary calcium intake (Ireland and Fordtran, 1973; Malm, 1958; Spencer et al., 1969). For example, when calcium intake was acutely lowered from 2,000 to 300 mg (50 to 7.5 mmol)/day, healthy women increased their fractional whole body retention of ingested calcium, an index of calcium absorption, from 27 percent to about 37 percent (Dawson-Hughes et al., 1993). This adaptation required 1 to 2 weeks and was accompanied by a decline in serum calcium and a rise in serum parathyroid hormone (PTH) and $1,25(OH)_2D$ concentrations. In general, the adaptive rise in the fraction of calcium absorbed as intake is lowered is not sufficient to offset the loss in absorbed calcium that occurs with a decrease in calcium intake, however modest that decrease. This is clear from the demonstrations that absorbed calcium and calcium intake, throughout a wide intake range, are positively related (Gallagher et al., 1980; Heaney et al., 1975).

Fractional calcium absorption varies through the lifespan. It is highest (about 60 percent) in infancy (Abrams et al., 1997a; Fomon and Nelson, 1993) and rises again in early puberty. Abrams and Stuff (1994) found fractional absorption in Caucasian girls consuming a mean of about 925 mg (23.1 mmol)/day of calcium to average 28 percent in prepubertal children, 34 percent in early puberty (the age of the growth spurt), and 25 percent 2 years later. Fractional absorption remains at about this value (25 percent) in young adults, with the exception that it increases during the last two trimesters of pregnancy (Heaney et al., 1989). With aging, fractional absorption gradually declines. In postmenopausal women, fractional absorption declined by an average of 0.21 percent/year (Heaney et al., 1989). Bullamore and colleagues (1970) reported that men lose absorption efficiency with aging at about the same rate as women.

Renal calcium excretion is a function of the filtered load and the

efficiency of reabsorption; the latter is regulated primarily by the PTH level. With aging, the urinary loss of calcium decreases (Davis et al., 1970), possibly because of an age-related decrease in intestinal calcium absorption efficiency and an associated reduction in filtered calcium load. Endogenous fecal calcium excretion does not change appreciably with aging (Heaney and Recker, 1994).

Racial differences in calcium metabolism have been noted in children and adults. In children and adolescents aged 9 to 18 years, Bell and colleagues (1993) found that African Americans had similar calcium absorption efficiency but lower urinary calcium excretion than Caucasians. Abrams and colleagues (1996a) found absorption efficiency to be similar in prepubertal African American and Caucasian girls or boys but greater in African American girls after menarche. In their study, urinary calcium excretion was lower in African American girls before menarche but similar in postmenarcheal African American and Caucasian girls. These metabolic differences may contribute to the widely observed higher bone mass in African American children (Bell et al., 1991; Gilsanz et al., 1991) and adults (Cohn et al., 1977; Liel et al., 1988; Luckey et al., 1989), and to lower fracture rates in African American adults in the United States (Farmer et al., 1984; Kellie and Brody, 1990). However, their implications for the calcium intake requirement are not clear, and observed differences do not warrant race-specific recommendations at this time.

Factors Affecting the Calcium Requirement

Bioavailability

When evaluating the food sources of calcium, the calcium content is generally of greater importance than bioavailability. Calcium absorption efficiency is fairly similar from most foods, including milk and milk products and grains (major food sources of calcium in North American diets). It should be noted that calcium may be poorly absorbed from foods rich in oxalic acid (spinach, sweet potatoes, rhubarb, and beans) or phytic acid (unleavened bread, raw beans, seeds, nuts and grains, and soy isolates). Soybeans contain large amounts of phytic acid, yet calcium absorption is relatively high from this food (Heaney et al., 1991). In comparison to calcium absorption from milk, calcium absorption from dried beans is about half and from spinach is about one tenth. Because diets used in metabolic studies and in the general population contain calcium from a variety of sources, and because the specific foods used in

most of the published studies were not described, adjusting for varying bioavailability was not considered in setting the calcium intake requirements.

Bioavailability of calcium when measured from nonfood sources, or supplements, depends on the presence or absence of a meal and the size of the dose. Supplement solubility is not very important (Heaney et al., 1990a), but tablet disintegration (for example, breaking apart) is essential (Whiting and Pluhator, 1992). In studies that measured calcium absorption under similar test conditions, a 250 mg (6.2 mmol) elemental calcium load given with a standardized breakfast meal resulted in average fractional absorption rates of calcium from calcium citrate malate, calcium carbonate, and tricalcium phosphate of 35, 27, and 25 percent, respectively (Heaney et al., 1989, 1990a; Miller et al., 1988; Smith et al., 1987). Under the same conditions, absorption of calcium from milk was similar at 29 percent. Individuals with achlorhydria absorb calcium from calcium carbonate poorly unless the supplement is taken with a meal (Recker, 1985). The efficiency of absorption of calcium from supplements is greatest when calcium is taken in doses of 500 mg (12.5 mmol) or less (Heaney et al., 1975, 1988).

Physical Activity

The concept that weight-bearing physical activity or mechanical loading determines the strength, shape, and mass of bone is generally accepted (Frost, 1987). The mechanisms by which exercise influences bone mass and structure are currently under investigation (Frost, 1997). Although exercise and calcium intake both influence bone mass, it is unclear whether calcium intake influences the degree of benefit derived from exercise. Under the extreme condition of immobilization, rapid bone loss occurs despite consumption of 1,000 mg (25 mmol)/day of calcium (LeBlanc et al., 1995). In a 3-year calcium intervention study in children aged 6 to 14 years, both calcium and exercise influenced the rate of bone mineralization, but their effects appeared to be independent (Slemenda et al., 1994). Specker (1996) reviewed published prospective exercise studies in which calcium intake data were provided. Sixteen studies were identified, 15 conducted in women and 1 in men. High daily calcium intakes (over 1,000 mg [25 mmol]) enhanced the bone mineral density (BMD) benefits from exercise at the lumbar spine, but enhancement at the radius was less pronounced. Additional prospective studies are needed to test and compare individual and combined effects of calcium and exercise.

Currently, there is insufficient evidence to justify different calcium intake recommendations for people with different levels of physical activity.

Nutrient-Nutrient Interactions

Sodium. Sodium and calcium excretion are linked in the proximal renal tubule. High sodium chloride intake results in increased absorbed sodium, increased urinary sodium, and an increased obligatory loss of urinary calcium (Kurtz et al., 1987). Quantitatively, 500 mg of sodium as sodium chloride has been shown to draw about 10 mg (0.25 mmol) of calcium into the urine in postmenopausal women (Nordin and Polley, 1987). This linkage holds at moderate and high calcium intakes, but some dissociation occurs at low calcium intakes (Dawson-Hughes et al., 1996), probably because low calcium intakes induce higher PTH levels, and PTH promotes the reabsorption of filtered calcium in the distal renal tubule. In children and adolescents, urinary sodium is an important determinant of urinary calcium excretion (Matkovic et al., 1995; O'Brien et al., 1996). An association between salt intake (or sodium excretion) and skeletal development has not been demonstrated in children or adolescents, but one longitudinal study in postmenopausal women identified a correlation between high urinary sodium excretion and increased bone loss from the hip (Devine et al., 1995). Thus, although indirect evidence indicates that dietary sodium chloride has a negative effect on the skeleton, the effect of a change in sodium intake on bone loss and fracture rates has not been reported. Although there is some concern related to the effects of the high salt content of American diets (from processed foods, etc.), available evidence does not warrant different calcium intake requirements for individuals according to their salt consumption.

Protein. Protein increases urinary calcium excretion, but its effect on calcium retention is controversial. In balance studies involving use of formula diets in which the phosphorus content was stable, 1 g of dietary protein from both animal and vegetable sources increased urinary calcium excretion by about 1 to 1.5 mg (Linkswiler et al., 1981; Margen et al., 1974). Walker and Linkswiler (1972) found that urinary calcium increased by about 0.5 mg for each gram of dietary protein, as protein intake increased above 47 g/day. In a recent study, a high protein intake (2.71 ± 0.75 g/kg/day) had no measurable effect on urinary pyridinium cross-links of collagen, an index of bone resorption (Delmas, 1992), in young adults consum-

ing 1,600 mg (40 mmol)/day of calcium, possibly because of the variability in this measure (Shapses et al., 1995). While dietary protein intake increases urinary calcium excretion, it should be recognized that inadequate protein intakes (34 g/day) have been associated with poor general health and poor recovery from osteoporotic hip fractures (Delmi et al., 1990). Similarly, serum albumin values have been shown to be inversely related to hip fracture risk (Huang et al., 1996). Available evidence does not warrant adjusting calcium intake recommendations based on dietary protein intake.

Other Food Components

Caffeine. Caffeine has a modest negative impact on calcium retention (Barger-Lux et al., 1990) and has been associated with increased hip fracture risk in women (Kiel et al., 1990). The association of caffeine consumption with accelerated bone loss has been limited to postmenopausal women with low calcium intakes (Harris and Dawson-Hughes, 1994). Specifically, associations with bone loss from the spine and total body were identified in women who consumed less than about 800 mg (20 mmol)/day of calcium and the amount of caffeine present in two or more cups of brewed coffee. Consistent with this is the observation that the negative effect of caffeine on BMD can be offset by the addition of dietary calcium (Barrett-Connor et al., 1994). Caffeine induces a short-term increase in renal calcium excretion (Massey and Wise, 1984) and may modestly decrease calcium absorption (Barger-Lux and Heaney, 1995); its effect on dermal calcium loss has not been evaluated. In summary, the skeletal effects of caffeine are modest at calcium intakes of 800 mg (20 mmol)/day and above. Available evidence does not warrant different calcium intake recommendations for people with different caffeine intakes.

Special Populations

Amenorrheic Women. Conditions that produce lower levels of circulating estrogen alter calcium homeostasis. Young women with amenorrhea resulting from anorexia nervosa have reduced net calcium absorption, higher urinary calcium excretion, and a lower rate of bone formation when compared with healthy eumenorrheic women (Abrams et al., 1993). Exercise-induced amenorrhea also results in reduced calcium retention and lower bone mass (Drinkwater et al., 1990; Marcus et al., 1985).

Menopausal Women. Decreased estrogen production at menopause is associated with accelerated bone loss, particularly from the lumbar spine, for about 5 years (Gallagher et al., 1987). During this period, women lose an average of about 3 percent of their skeletal mass per year. Lower levels of estrogen are accompanied by decreased calcium absorption efficiency (Gallagher et al., 1980; Heaney et al., 1989) and increased rates of bone turnover. These observations may be interpreted several ways. First, lowered estrogen levels primarily affect the skeleton, leading to increased bone resorption, an increase in circulating ionized calcium, a decrease in $1,25(OH)_2D$, and reduced stimulus for active intestinal transport of calcium (Gallagher et al., 1980). A second interpretation is that estrogen deficiency primarily reduces the efficiency of dietary calcium utilization and that this reduced efficiency produces a bone loss related to calcium substrate deficiency (Gallagher et al., 1980). A third interpretation is that estrogen has primary effects on both bone and the intestine. The impact on what the dietary calcium intake should be to meet requirements in the above scenarios differs. Increasing calcium intake would provide little skeletal benefit if the primary effect of estrogen withdrawal is at the skeleton. That is, increasing calcium intake would increase absorbed calcium but not the deposition of calcium in bone. The excess absorbed calcium would be excreted in the urine. In contrast, increasing calcium intake should correct the problem (for example, prevent bone loss) if estrogen deficiency primarily reduces calcium absorption efficiency.

Examination of the skeletal response to calcium supplementation in premenopausal and early postmenopausal women provides some insight. In a longitudinal calcium supplement trial in women aged 46 to 55 years, Elders et al. (1994) found that 2,000 mg (50 mmol)/day of supplemental calcium significantly reduced bone loss from the lumbar spine in premenopausal women but not in the early postmenopausal women. The effect of calcium supplementation on metacarpal cortical thickness was not significantly related to the menopausal status of the women in this study. In a different study of women with low usual calcium intakes, supplementation with 500 mg (12.5 mmol)/day of calcium had no significant impact on bone loss from the spine or other sites in early postmenopausal women, but it significantly reduced bone loss in women more than 5 years beyond menopause (Dawson-Hughes et al., 1990). From these and other studies (Aloia et al., 1994; Prince et al., 1991; Riis et al., 1987) (see Table 4-1), it is apparent that increasing calcium intake will not prevent the rapid trabecular bone loss that occurs in the first 5 years after menopause. Calcium responsiveness of cortical bone

TABLE 4-1 Randomized Controlled Calcium Intervention Trials in Postmenopausal Women

Site	N	Calcium Intake (mg/day) Diet	Supplement[a]	Relative Change in BMD or BMC in Calcium Group Compared with Placebo Year 1	Year 2 or More, Annualized	Statistically Significant Change in BMD or BMC in Calcium Group Compared with Placebo
Spine						
Early postmenopausal						
Aloia et al., 1994[b]	70	500	1,700	P[j]	S or N	no
Dawson-Hughes et al., 1990	67	<400	500	S[h] or N[i]	S	no
Elders et al., 1991[d]	248	1,150	1,000 and 2,000	P	S or N	yes
Riis et al., 1987	25	~1,000[c]	2,000	P	S or N	no
Late Menopausal						
Dawson-Hughes et al., 1990	169	<400	500 (CCM)	P	S or N	yes
			500 (CC)	P	S or N	no
		400–650	500 (CCM)	P	S or N	no
			500 (CC)	S or N	S or N	no
Prince et al., 1995	126	800	1,000	P	S or N	no
Reid et al., 1995	78	750	1,000	P	S or N	yes
Radius (Proximal)						
Early postmenopausal						
Aloia et al., 1994[b]	70	500	1,700	S or N	P	no
Dawson-Hughes et al., 1990	67	<400	500	P	P	no
Prince et al., 1991[e]	80	800	1,000	P	P	no
Riis et al., 1987	25	~1,000	2,000	P	P	yes
Late postmenopausal						
Dawson-Hughes et al., 1990	169	<400	500 (CCM)	P	P	yes
			500 (CC)	P	S or N	yes
		400–650	500 (CCM)	P	P	no
			500 (CC)	P	P	no
Recker et al., 1996: Prevalent vertebral fracture group	94	~450	1,200 (CC)	—	—	yes
Non-prevalent vertebral fracture group	99	~450	1,200 (CC)	—	—	no

TABLE 4-1 Continued

Site	N	Calcium Intake (mg/day) Diet	Supplement[a]	Relative Change in BMD or BMC in Calcium Group Compared with Placebo Year 1	Year 2 or More, Annualized	Statistically Significant Changes in BMD or BMC in Calcium Group Compared with Placebo
Femoral neck						
Early postmenopausal						
Aloia et al., 1994[b]	70	500	1,700	P	P	yes
Dawson-Hughes et al., 1990	67	<400	500	P	S	no
Late menopausal						
Chevalley et al., 1994	93	600	800	P[f]		no
Dawson-Hughes et al., 1990	169	<400	500 (CCM)	P	P	yes
			500 (CC)	P	P	no
		400–650	500 (CCM)	P	S or N	no
			500 (CC)	P	S or N	no
Prince et al., 1995[g]	126	800	1,000	P	P	no
Reid et al., 1995	78	750	1,000	P	S or N	yes
Total Body						
Early postmenopausal						
Aloia et al., 1994[b]	70	500	1,700	P	P	yes
Late postmenopausal						
Reid et al., 1995	78	750	1,000	P	P	yes

[a] Calcium sources: Dawson-Hughes: citrate malate (CCM), carbonate (CC); Aloia, Ettinger, and Riis: CC; Prince: lactate-gluconate (1991, 1995), milk powder (1995); Elders and Reid: (lactate-gluconate + CC) or citrate; Chevalley: CC or osseino-mineral complex.

[b] All women treated with 400 IU (10 µg) vitamin D per day.

[c] Estimate based on national norm rather than on intake of study subjects.

[d] Randomized open trial.

[e] All women participated in exercise program.

[f] An 18-month study in 82 women and 11 men.

[g] Supplement tablets and milk powder significantly reduced bone loss at the trochanter.

[h] S = Similar change in BMD or BMC when compared with placebo.

[i] N = Negative, but not necessarily significant, change in BMC or BMD when compared with placebo.

[j] P = Positive, but not necessarily significant, change in BMC or BMD when compared with placebo.

SOURCE: Adapted, with permission, from Dawson-Hughes B. ©1996. Calcium. In: Marcus R, Feldman D, Kelsey J, eds. *Osteoporosis.* San Diego: Academic Press, Inc. Pp. 1103 and 1105.

appears to be less dependent on menopausal status. In summary, from available evidence, the calcium intake requirement for women does not appear to change acutely with menopause.

Lactose Intolerance. About 25 percent of adults in the United States have lactose intolerance and develop symptoms of diarrhea and bloating after ingestion of a large dose of lactose, such as the amount present in a quart of milk (about 46 g) (Coffin et al., 1994). Primary lactase deficiency begins in childhood and may become clinically apparent in adolescence. In adults, the prevalence of lactose intolerance, as estimated by a positive breath-hydrogen test, is highest in Asians (about 85 percent), intermediate in African Americans (about 50 percent), and lowest in Caucasians (about 10 percent) (Johnson et al., 1993a; Nose et al., 1979; Rao et al., 1994). Lactose-intolerant individuals often avoid milk products entirely although avoidance may not be necessary. Studies have revealed that many lactose-intolerant people can tolerate smaller doses of lactose, for example, the amount present in an 8 oz glass of milk (about 11 g) (Johnson et al., 1993b; Suarez et al., 1995). In addition, lactose-free dairy products are available. Although lactose-intolerant individuals absorb calcium normally from milk (Horowitz et al., 1987; Tremaine et al., 1986), they are at risk for calcium deficiency because of avoidance of milk and other calcium-rich milk products. Although lactose intolerance may influence intake, there is no evidence to suggest that it influences the calcium requirement.

Vegetarian Diets. Consumption of vegetarian diets may influence the calcium requirement because of their relatively high contents of oxalate and phytate, compounds that reduce calcium bioavailablity. In contrast to diets containing animal protein, however, vegetarian diets produce metabolizable anions (for example, acetate, bicarbonate) that lower urinary calcium excretion (Berkelhammer et al., 1988; Sebastian et al., 1994). On balance, lacto-ovovegetarians and omnivores appear to have fairly similar dietary calcium intakes (Marsh et al., 1980; Pedersen et al., 1991; Reed et al., 1994) and, on the same intakes, to have similar amounts of urinary calcium excretion (Lloyd et al., 1991; Tesar et al., 1992). BMD has been examined and compared in several cross-sectional studies of lacto-ovovegetarians and omnivores. Among premenopausal women, spinal BMD did not differ significantly in the two groups (Lloyd et al., 1991). Postmenopausal lacto-ovovegetarians are reported to have higher cortical bone mass than omnivores, as indicated by higher midradius density (Marsh et al., 1980; Tylavsky and Anderson,

1988). However, in a 5-year study, postmenopausal lacto-ovovegetarians and omnivores with similar calcium intakes lost radius BMD at similar rates (Reed et al., 1994). Bone data on strict vegetarians (vegans) are not available, but there is evidence in this group to indicate lower intakes of calcium (among other nutrients) in premenopausal women (Janelle and Barr, 1995), and lower body weight in children (Sanders and Purves, 1981). In conclusion, available data do not support the need for a different calcium intake recommendation for vegetarians.

Intake of Calcium

The USDA 1994 Continuing Survey of Food Intakes by Individuals (CSFII), showed that mean daily calcium intake, based on an adjusted 24-hour recall which allows for varying degrees of departure from normality and recognizes the measurement error associated with one-day dietary intakes (Nusser et al., 1996), was about 25 percent higher in males than in females aged 9 years and older in the United States (925 vs. 657 mg [23.1 vs. 16.4 mmol]) (Cleveland et al., 1996) (see Appendix D for data tables). The fifth percentiles of intake from the 1994 CSFII for males and females aged 9 and over were 431 and 316 mg (10.8 and 7.9 mmol)/day. The corresponding median intake was 865 and 625 mg (21.6 and 15.6 mmol)/day and the ninety-fifth percentile intakes were 1,620 and 1,109 mg (40.5 and 27.7 mmol)/day. In males, daily intake peaked in the age range of 14 through 18 years (at 1,094 mg [27.4 mmol]) whereas it was highest in females aged 9 through 13 years (at 889 mg [22.2 mmol]). After age 50, median daily calcium intake remained almost constant for males aged 71 and above (708 to 702 mg [17.7 to 17.6 mmol]) and declined for women (571 to 517 mg [14.3 to 12.9 mmol]). Data from the first phase of the Third National Health and Nutrition Examination Survey (NHANES III) are similar (Alaimo et al., 1994). Unfortunately, national survey data from Canada are not currently available.

Food Sources of Calcium

According to data for 1994, 73 percent of calcium in the U.S. food supply is from milk products, 9 percent is from fruits and vegetables, 5 percent is from grain products, and the remaining 12 percent is from all other sources (CNPP, 1996). Grains are not particularly rich in calcium, but because they may be consumed in large quantities, they can account for a substantial proportion of

dietary calcium. Among Mexican American adults, corn tortillas are the second most important food source of calcium, after milk (Looker et al., 1993), but calcium from tortillas may be poorly absorbed (Rosado et al., 1992). White bread is the second most important source among Puerto Rican adults (Looker et al., 1993). Milk products, the most calcium-dense foods in Western diets, contain about 300 mg (7.5 mmol) calcium per serving (for example, per 8 oz of milk or yogurt or 1.5 oz of cheddar cheese). Other calcium-rich foods include calcium-set tofu, Chinese cabbage, kale, calcium-fortified orange juice, and broccoli.

Calcium Intake from Supplements

Results from a National Health Interview Survey (NHIS) in 1986 show that almost 25 percent of women in the United States took supplements containing calcium (Moss et al., 1989). Usage by men (14 percent) and children 2 to 6 years of age (7.5 percent) was less. Women who used supplements also took higher doses (median of 248 mg [6.2 mmol]/day) than men who used supplements (160 mg [4 mmol]/day). Children who took supplements had a median supplemental intake of only 88 mg (2.2 mmol)/day. The ninety-fifth percentile of supplemental intake was 304 mg (7.6 mmol)/day for young children, 928 mg (23.2 mmol)/day for men, and 1,200 mg (30 mmol)/day for women.

Data from 11,643 adults who participated in the 1992 NHIS show that calcium intakes are higher for both men and women who take dietary supplements (of any kind) daily than those who seldom or never take them, but the differences are statistically significant only for women (Slesinski et al., 1996). However, those adults who specifically take calcium supplements do not have higher intakes of food calcium.

Effects of Inadequate Calcium Intake

Chronic calcium deficiency resulting from inadequate intake or poor intestinal absorption is one of several important causes of reduced bone mass and osteoporosis (DHHS, 1990; NIH, 1994; NRC, 1989b; Osteoporosis Society of Canada, 1993). A reduction in absorbed calcium causes the circulating ionized calcium concentration to decline, which triggers an increase in PTH synthesis and release. PTH acts on three target organs to restore the circulating calcium concentration to normal. At the kidney, PTH promotes the reabsorption of calcium in the distal tubule. PTH affects the

intestine indirectly by stimulating the production of $1,25(OH)_2D$. PTH also induces bone resorption, thereby releasing calcium into the blood. Thus, although PTH maintains a normal circulating calcium concentration during calcium deprivation, it does so at the expense of skeletal mass.

Dietary Calcium and Osteoporosis

Osteoporosis is characterized by reduced bone mass, increased bone fragility, and increased risk of fracture (WHO, 1994). According to the World Health Organization (WHO), individuals with BMD more than 2.5 standard deviations (SD) below the mean for young adult women are *osteoporotic* (Kanis et al., 1994; WHO, 1994). By this definition, the prevalence of osteoporosis among postmenopausal women in the United States is 21 percent in Caucasian and Asian, 16 percent in Hispanic, and 10 percent in African American women (Looker et al., 1995). An additional 38 percent of American women aged 50 and older meet the WHO definition of *osteopenic* (for example, have BMD values 1.0 to 2.5 SD below the young adult reference mean) (Looker et al., 1995).

In the United States each year, approximately 1.5 million fractures are associated with osteoporosis, including 300,000 hip fractures, 700,000 vertebral fractures, 250,000 distal forearm fractures, and 250,000 fractures at other sites (Riggs and Melton, 1995). In Canada in 1993, approximately 76,000 fractures were associated with osteoporosis, including 21,000 hip fractures, 27,000 vertebral fractures, and 27,000 wrist fractures (Goeree et al., 1996). Incidence rates for most fractures rise exponentially with age (Cooper and Melton, 1992). For individuals at age 50, their risk of having a hip fracture at some point in the future is estimated at 17 percent for Caucasian women, 6 percent for African American women, 6 percent for Caucasian men, and 3 percent for African American men (Cummings et al., 1993; Melton et al., 1992). It has been estimated that a Caucasian woman's risk of a hip fracture is equivalent to her combined risk of developing breast, uterine, and ovarian cancer (Riggs and Melton, 1995). Health care costs associated with osteoporotic fractures in 1995 were estimated at $13.8 billion (Ray et al., 1997). Because of the expected increase in the number of individuals in the age range of highest risk, the incidence of hip fractures in the United States may triple by the year 2040 (Schneider and Guralnik, 1990).

ESTIMATING REQUIREMENTS FOR CALCIUM

Selection of Indicators for Estimating the Calcium Requirement

There is no biochemical assay that reflects calcium nutritional status. Blood calcium concentration, for example, is not a good indicator because it is tightly regulated. Only in extreme circumstances, such as severe malnutrition or hyperparathyroidism, is the serum ionized calcium concentration below or above the normal range. Search of the scientific literature reveals numerous potential indirect indicators of calcium adequacy, most of which are closely related to the skeletal calcium content.

Calcium Intake and Fracture Risk

Ideally, the optimal calcium intake for skeletal health would be defined as that which leads to the fewest osteoporotic fractures later in life. Attaining this information would require prospective determination of the influence of different increments in calcium intake on fracture rates in young and older subjects with a wide range of usual calcium intakes. Such studies are not available, would require that large numbers of subjects be studied for many years, and would be prohibitively expensive.

Several observational studies of calcium intake and fracture risk are available (Cumming et al., 1997; Cummings et al., 1995; Holbrook et al., 1988; Looker et al., 1993; Paganini-Hill et al., 1991; Wickham et al., 1989). Among these, no consistent association has been demonstrated between reported calcium intake over periods of up to 10 years and risk of fracture in peri- and postmenopausal women (Cumming et al., 1997). This is not surprising because osteoporosis results from complex interactions among genetic, dietary, and other environmental factors and has a long latency period. From a methodologic perspective, calcium intake may be underestimated by some survey methods and overestimated by others. More importantly, even if accurate estimates of calcium intake were available, intakes measured at one point in time do not reflect lifetime consumption. In addition, the influence of confounding factors such as frequency of falls and physical activity may vary over time. For these reasons observational studies cannot be used effectively to determine an Estimated Average Requirement (EAR) for calcium.

Another approach that has been attempted is to compare fracture rates across cultures that have different calcium intakes. This

approach however, is severely limited by cross-cultural differences in bone structural features, genetic composition, diets (nutrients other than calcium), and other environmental factors that influence fracture rates. For example, a longer hip axis length (the distance from the greater trochanter to the inner pelvic brim [HAL]) is associated with an increased hip fracture incidence (Faulkner et al., 1993). Japanese women have shorter HALs than Caucasian Americans and this may partially account for why their hip fracture rates are lower (Nakamura et al., 1994). Genetic differences related to calcium homeostasis may also thwart efforts to estimate calcium requirements from cross-cultural studies. The prevalence of a vitamin D-receptor-gene genotype associated with reduced calcium absorption efficiency (Dawson-Hughes et al., 1995) is lower in Japanese women than in Caucasian American women (Yamagata et al., 1994). Finally, many environmental factors differ more between cultures than within cultures and these differences are not controlled for when independently conducted studies are compared. Thus the use of observational studies relating intakes to fracture risk as the primary determinant of requirements is not warranted at this time.

Bone Mass Measurements

Bone mineral content (BMC) is the amount of mineral at a particular skeletal site such as the femoral neck, lumbar spine, or total body. *Bone mineral density* (BMD) is BMC divided by the area of the scanned region. Recent studies have indicated that both measures are strong predictors of fracture risk (Black et al., 1992; Cummings et al., 1993; Melton et al., 1993a). In adults, a 1 standard deviation (SD) decrease (representing about a 15 percent decline) in femoral neck BMD is associated with a 2.5-fold increase in risk of hip fracture (Cummings et al., 1993). A 1 SD decrease in lumbar spine BMD increases vertebral fracture risk two fold (Cummings et al., 1993).

BMD and BMC are both measured by a variety of related techniques including dual-energy x-ray absorptiometry (DXA). The DXA method is precise, reasonably accurate, and, in the context of longitudinal calcium intervention trials that measure *change in BMC*, can provide data on the long-term impact of added calcium not only on the total skeleton but also on skeletal sites that are subject to osteoporotic fractures. In children, change in BMC is a useful indicator of calcium retention, but change in BMD is less suitable than BMC because BMD misses much of the change in skeletal size.

In adults, with their generally stable skeletal size, change in both BMD and BMC are useful outcome measures. The ability of DXA to measure specific skeletal regions such as the spine, hip, and forearm adds a potentially valuable refinement to the determination of the calcium requirement derived from balance studies (see "Calcium Retention" below). This technique has already revealed that the patterns and timing of acquisition of peak bone mass vary by skeletal site, and that bone loss from trabecular- and cortical-rich sites occurs at different rates in women at menopause (see Table 4-1). Available evidence from supplementation trials in postmenopausal women also suggests that the calcium intake needed for maximal bone preservation differs by skeletal site (see Table 4-1). This is addressed more specifically in the section on requirements for adults over age 50.

Calcium Intake and Bone Mass

Cross-sectional studies that relate dietary calcium intake to BMC or BMD are of modest value in establishing the calcium requirement. These studies are of limited value because calcium intake is not accurately measured, calcium intake at one point in time may not reflect lifetime calcium intake, and bone mass at a single point in time is the result of the lifelong influence of many confounding variables that are not measured.

In contrast, randomized, placebo-controlled calcium intervention studies that measure change in BMC or BMD provide valuable evidence for the calcium requirement. A major strength of such longitudinal studies is that the increment in calcium intake (the intervention) is known. In addition, their generally large sample sizes and subject randomization greatly reduce confounding of the results by other factors that influence bone mass. Limitations are that they require large sample sizes, are very expensive, and usually test only one or two doses of calcium per study. Assessment of dietary calcium intake (in contrast to the intervention) is subject to the usual inaccuracies.

An important consideration in the interpretation of longitudinal calcium intervention studies is the phenomenon of the *bone remodeling transient*, the one-time initial gain in bone mass that occurs in the first 3 to 12 months after increasing calcium intake (or administration of an antiresorptive drug) (Frost, 1973). Calcium supplementation trials of 1 to 2 years duration may overestimate the longer-term influence of calcium because of the effect of calcium (and all remodeling suppressers) in reducing the size of the remodeling

space, the portion of total bone mass that is currently being remodeled. The remodeling rate in trabecular bone is four to five times greater than that in cortical bone. As a result, the remodeling transient is more apparent at the more highly trabecular spine than it is at the more cortical radius or the even more dominantly cortical total skeleton. Because of the bone remodeling transient, the long-term or cumulative effect of calcium can best be evaluated by examining the effect of added calcium in the second and later years of an intervention (Table 4-1).

Calcium Retention

In estimating the intake requirement for calcium, it is important to recognize that calcium is unique in several respects. First, 99 percent of body calcium is located in the skeleton which has an essential structural function. To maximize skeletal size and strength, one must have adequate calcium retention to provide the substrate (along with other minerals) for bone mineral expansion during growth and maintenance after peak bone mass has been achieved. To a great extent, the retention of calcium in bone is under strong homeostatic control, which is regulated by genetics, calciotropic hormones and weight bearing exercise. The target intake of dietary calcium to achieve the desirable and optimal calcium accretion in bone is difficult to estimate because of all of the other factors which play a role in bone mineral homeostasis.

In this report, classic metabolic studies of calcium balance were used to obtain data on the relationship between calcium intakes and retention from which a non-linear regression model was developed; and from this was derived an intake of calcium which would be adequate to attain a predetermined *desirable* calcium retention. This approach is a further refinement of an earlier approach suggested to determine the point at which additional calcium does not significantly increase calcium retention, called the *plateau intake* (Matkovic and Heaney, 1992; Spencer et al., 1984).

The predetermined desirable calcium retentions for adolescents and young adults were based on estimates of the calcium accretion in bone over either four years of adolescence or during the 3rd decade of life, to which were added estimates for sweat and other losses if not included in the experiment. For older adults, a value approximating zero balance was used for desirable retention assuming that no net positive accretion of bone at this age in replete individuals serves a functional advantage. Adults continue to lose bone despite high intakes of calcium for other reasons such as lack

of estrogen, smoking, or sedentary lifestyle. Thus not all bone loss can be prevented by additional dietary calcium.

The balance studies used in this report were reviewed rigorously to meet specific criteria which included the following: subjects consumed a wide range of calcium intakes since variability in retention increases at higher intakes; the balance studies were initiated at least 7 days after starting the diet in order for subjects to approach a steady state as observed by Dawson-Hughes et al. (1988); and, where possible, the adult balance studies included were only for subjects who were consuming their usual calcium intakes unless otherwise indicated. By selecting studies conducted on such subjects, it obviates the concern about whether the *bone remodeling transient* might introduce bias in the calcium retentions observed. Such selection was not possible in studies in children where they have been randomized to one of two calcium intakes. However, in children the impact of the remodeling transient related to changing intake is overshadowed by their rapid and constantly changing rates of calcium accretion (for example, their modeling and remodeling rates are not in steady state even without an intake change).

The non-linear regression model describing the relationship between calcium intake and retention was solved to obtain a predicted calcium intake for a predetermined desirable calcium retention[1] which was specific for each age group. The basis of the value

[1] The Panel on Calcium and Related Nutrients proposed use of a recently described statistical model (Jackman et al., 1997) to estimate an intake necessary to support maximal calcium retention and from which to derive an EAR. In the original paper by Jackman et al. (1997), an estimate was made of the lowest level of calcium intake that was statistically indistinguishable from 100 percent maximal retention in some individuals. However, the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes (DRI Committee) adopted a different interpretation of the data for the purpose of establishing an AI. The approach adopted is described in the prepublication version of this final report. The DRI Committee was subsequently advised that there were both statistical and biological concerns with the application of the percent maximal retention model (see Appendix E). After seeking input from the Panel on Calcium and Related Nutrients, the DRI Committee has chosen, for the final print of the report, to retain the statistical model described by Jackman et al. (1997), but to apply it to determine, from the same calcium balance data as was used in the prepublication report, an estimate of the calcium intake that is sufficient to achieve a defined, desirable level of calcium retention specific to the age groups considered. The mathematical modeling and basis of the equations were kindly provided for the report by Dr. George McCabe and Dr. Connie Weaver of Purdue University and are described in detail in Appendix E.

used for desirable calcium retention is delineated under each age-specific group. In general, for growing children and young adults, data on whole body bone mineral accretion using DXA technology were used to derive a value for calcium retention to support the reported bone accretion (assuming bone is 32.3 percent calcium). The major limitation of the data available is that bone mineral accretion during growth has not been studied over a wide range of calcium intakes.

Calcium Intake and Risk of Chronic Disease Other than Osteoporosis

Hypertension. Many studies have investigated a possible role of calcium in lowering the risk of hypertension. In a review of 22 randomized intervention trials, calcium supplementation was found to reduce systolic blood pressure modestly—by 1.68 mm Hg in hypertensive adults—and had no significant effect in normotensive adults (Allender et al., 1996). Diastolic blood pressure was not altered in either group. More recently, a diet with increased low-fat dairy products, fruits, and vegetables, and with reduced saturated and total fat, lowered blood pressure when fed to normotensive and hypertensive adults (Appel et al., 1997). In this study, the increase in dairy product consumption provided a mean dietary calcium increase from 443 to 1,265 mg (11.1 to 31.6 mmol)/day.

Little is known about the relationship of calcium intake and blood pressure in children. A recent randomized trial on 101 boys and girls with mean age 11 years (9.9 to 13.2 years) of African American, Caucasian, Asian, and Hispanic origin showed that calcium supplementation of 600 mg (15 mmol)/day could reduce blood pressure, although the effect was much larger in children who had lower baseline calcium intakes (150 to 347 mg [3.7 to 8.7 mmol]/1,000 kcal) (Gillman et al., 1995). No further reduction in blood pressure was observed in children already consuming over 1,000 mg (25 mmol)/day of calcium by supplementing them with 600 mg (15 mmol)/day.

The influence of dietary calcium on pregnancy-induced hypertension has been investigated extensively. A meta-analysis of 14 randomized controlled trials of calcium supplementation during pregnancy found that supplements of 1,500 to 2,000 mg (37.5 to 50 mmol)/day of calcium may result in a significant lowering of both diastolic and systolic blood pressure (Bucher et al., 1996). However, the randomized controlled trial of Calcium for Preeclampsia Prevention (CPEP) in 4,589 pregnant women found no effect of

calcium supplementation on hypertension, blood pressure, or preeclampsia (Levine et al., 1997), perhaps because the intake of the control group was above a threshold value. In that study, women in the placebo group had a mean intake of 980 mg (24.5 mmol)/day and women in the supplemental calcium group had a mean intake of 2,300 mg (57.5 mmol)/day.

Because the effect of dietary calcium on blood pressure may be modest and variable in the general population, and because the calcium intake needed to reduce blood pressure is very likely below the threshold necessary for desirable skeletal retention (McCarron et al., 1991), blood pressure will not be used as a primary indicator for estimating calcium requirements.

Colon Cancer. Colon cancer risk has been postulated as being influenced by dietary calcium intake, but the evidence is inconsistent. Bostick and colleagues (1993) reported a reduction in mucosal proliferation after calcium supplementation, whereas Kleibeuker and colleagues (1993) reported an increase. Greater mucosal proliferation has been observed in patients known to be at high risk of colon cancer as compared with those at low risk (Kanemitsu et al., 1985; Ponz de Leon et al., 1988; Roncucci et al., 1991). Data from observational and case-control studies are mixed (Garland et al., 1985; Meyer and White, 1993; Slattery et al., 1988), and prospective trials examining the effect of added calcium on colon cancer incidence are not available. Thus, colon cancer incidence is not a useful indicator for estimating calcium requirements at this time.

Limitations of the Evidence

In reviewing the scientific literature to provide the best estimate of calcium requirements for each stage of the lifespan, needed data were not always available. In most instances, calcium intake data could not be matched with the outcome criteria of both calcium retention and bone mass in the same subjects. For many of the age groups, available data did not adequately represent both genders and various ethnic groups. Although lower fracture rates have been reported in African American adults compared to those estimated in Caucasian adults (Farmer et al., 1984; Kellie and Brody, 1990) and in men compared to women (Cummings et al., 1993; Melton et al., 1992), the implications for calcium intake requirements are not clear at the present time. Because there is no sound basis for assigning different intake values according to gender or race/ethnic groups, findings have been extrapolated from one gender group to

another and from a predominantly Caucasian population to other ethnic groups.

Summary

Desirable rates of calcium retention, determined from balance studies, factorial estimates of requirements, and limited data on BMD and BMC changes, will be used as the primary indicators of adequacy. These indicators will be used as reasonable surrogate markers to reflect changes in skeletal calcium content.

The decision to set AIs for calcium rather than EARs was based on the following concerns: (1) uncertainties in the methods inherent in and the precise nutritional significance of values obtained from the balance studies that form the basis of the desirable retention model; (2) the lack of concordance between observational and experimental data (mean calcium intakes in the United States and Canada are much lower than are the experimentally derived values predicted to be required to achieve a desirable level of calcium retention); and (3) the lack of longitudinal data that could be used to verify the association of the experimentally derived calcium intakes for achieving a predetermined level of calcium retention with the rate and extent of long-term bone loss and its clinical sequelae, such as fracture. Taking all of these factors into consideration, it was determined that an EAR for calcium could not be established at the present time. The recommended AI represents an approximation of the calcium intake that, in the judgment of the DRI Committee, would appear to be sufficient to maintain calcium nutriture while recognizing that lower intakes may be adequate for some, but this evaluation will have to await additional studies on calcium balance over broad ranges of intakes and/or of long-term measures of calcium sufficiency.

FINDINGS BY LIFE STAGE AND GENDER GROUP

Birth through 12 Months

Indicators Used to Set the AI

There are no functional criteria for calcium status that reflect response to dietary intake in infants. Thus recommended intakes of calcium are based on an *adequate intak*e (AI) that reflects the derived mean intake of infants fed principally with human milk.

Human Milk. Human milk is recognized as the optimal source of nourishment for infants throughout at least the first year of life, and as a sole nutritional source for infants during the first 4 to 6 months of life (IOM, 1991). Further, there are no reports of full-term infants, who are exclusively and freely fed human milk and are vitamin D replete, who manifest any incidence of calcium deficiency. Therefore, consideration of the AI for calcium for infants is based on mean intake data from infants fed human milk as the principal fluid during the first year of life. This value was derived from studies where intake of human milk was measured by test weighing and where intake of food and formula by dietary records was determined for 3 days or more.

The concentration of calcium in human milk remains relatively constant, with a mean value of 264 mg (6.6 mmol)/liter throughout the first 6 months of nursing and with a small decrease during the second 6 months to about 210 mg (5.2 mmol)/liter (Atkinson et al., 1995). Variations in milk calcium content have been found between population groups. For example, in comparison with the above data from the United States, milk calcium concentrations were lower (by approximately 20 mg (0.5 mmol)/100 ml at 5 months of lactation) in mothers from the Gambia who usually have diets low in calcium (Prentice et al., 1995). Thus, for establishing values of milk calcium to use in setting the AIs, only studies on milk calcium from North America and the United Kingdom were considered to obtain a mean value.

Balance. Recently, calcium absorption using stable isotopes (Abrams et al., 1997a) was measured in 14 human milk-fed infants who were 5 through 7 months of age at the time of the study. Mean absorption was 61 ± 22 percent of intake when approximately 80 percent of the dietary calcium was from human milk. There was no significant relationship between calcium from solid foods and the fractional calcium absorption from human milk. This finding suggests that calcium from solid foods does not negatively affect the bioavailability of calcium from human milk. Using measured urinary calcium and estimates of endogenous excretion, net retention was calculated to be 68 ± 38 mg (1.7 ± 0.95 mmol)/day of calcium for those infants. At 61 percent calcium absorption from intake of the AI, this observed net retention (assuming small urinary and endogenous calcium losses) would easily be attained by infants fed the mixed diet of human milk and solid food.

Accretion. Total body calcium at birth in healthy, full-term infants

is approximately 30 g (750 mmol) (Widdowson et al., 1951). Based on mineral accretion derived as a function of change in body weight, total body calcium increases to approximately 80 g (2,000 mmol) by 1 year of age (Leitch and Aitken, 1959). This change would lead to an average accretion rate of approximately 140 mg (3.5 mmol)/day during the first year of life. This greatly exceeds the accretion rate of approximately 30 to 35 mg (0.75 to 0.87 mmol)/day from 0 through 4 months of age and 50 to 55 mg (1.25 to 1.37 mmol)/day from 4 through 12 months of age derived from cadaveric sources (Fomon and Nelson, 1993; Koo and Tsang, 1997). A mean accretion rate of approximately 80 mg (2 mmol)/day during the first year of life was derived using metacarpal morphometry data (Garn, 1972; Weaver, 1994). Resolution of these different values for usual accretion rate is not currently possible.

Differences in calcium needs between infants fed human milk and those fed infant formula are discussed in the "Special Considerations" section.

0 through 6 Months

The AI for infants 0 through 6 months of age is based on the reported intake of milk (780 ml/day) determined by test weighing of full-term infants in three studies (Allen et al., 1991; Butte et al., 1984; Heinig et al., 1993) and by the reported average calcium concentration in human milk after 1 month of lactation of 264 mg (6.6 mmol)/liter (average of 10 studies from the United States and the United Kingdom as summarized in Atkinson et al. [1995]). Total calcium intake may be somewhat lower during the first month of life than in subsequent months because of a lower total volume of milk intake (Lonnerdal, 1997; Southgate et al., 1969; Widdowson, 1965). Using the mean value for intake of human milk of 780 ml/day and the average content of 264 mg (6.6 mmol)/liter of calcium, the AI for calcium is 210 mg (5.3 mmol)/day. The expected net retention of calcium from human milk assuming 61 percent absorption would be 128 mg (3.2 mmol)/day, which is in excess of the values predicted from calcium accretion based on cadaver and metacarpal analysis. This provides evidence that an AI of 210 mg (5.3 mmol)/day will result in retention of sufficient amounts of calcium to meet growth needs.

For infants in the first 4 months of life, balance studies suggest that 40 to 70 percent of the daily calcium intake is retained by the human milk-fed infant (Fomon and Nelson, 1993; Widdowson, 1965). In balance studies in human milk-fed infants, a mean calci-

um intake was 327 mg (8.2 mmol)/day, and the retention was 80 mg (2 mmol)/day (Fomon and Nelson, 1993). If infants consume the daily estimated AI, they would achieve a similar or greater calcium retention even if the efficiency of absorption was at the lower observed value of 40 percent. Thus, the AI should meet most infants' needs.

7 through 12 Months

During the 7- through 12-month age period, the intake of solid foods becomes more significant, and calcium intakes may increase substantially from these sources. Although limited data are available for typical calcium intakes from foods by human milk-fed older infants, mean calcium intakes from solid foods are 140 mg (3.5 mmol)/day for formula-fed infants (Abrams et al., 1997a; Specker et al., 1997). For the purpose of developing an AI for this age group, it is assumed that infants who are fed human milk have intakes of solid food similar to formula-fed infants of the same age (Specker et al., 1997). Based on data of Dewey et al. (1984), mean human milk intake during the second six months of life would be 600 ml/day. Thus, calcium intake from human milk with a calcium concentration of about 210 mg (5.3 mmol)/liter during this age span (Atkinson et al., 1995) would be approximately 130 mg (3.2 mmol)/day. Adding the intake from milk (130 mg [3.2 mmol]) and food (140 mg [3.5 mmol]), the total AI for calcium is 270 mg (6.8 mmol)/day.

In the presence of adequate supplies of vitamin D from the environment or supplemental sources, there is no evidence of calcium deficiency in the human milk-fed infant during the first year of life (Mimouni et al., 1993). How much the AI of 270 mg (6.8 mmol)/day could be lowered and still meet the physiological needs for human milk-fed infants is unknown since mechanisms for adaptation to lower intakes of calcium are not well described for the infant population.

AI for Infants	**0 through 6 months**	**210 mg (5.3 mmol)/day**
	7 through 12 months	**270 mg (6.8 mmol)/day**

Special Considerations

Infant Formulas. Intake of calcium from infant formulas may need to be greater than from human milk in order to achieve the same retention since absolute fractional absorption of calcium from cow

milk or other formula may be lower than from human milk. Studies by Fomon and Nelson (1993) involving 40 human milk-fed, 252 cow milk formula-fed, and 135 soy protein formula-fed infants found absorption fractions of 58, 38, and 34 percent, respectively, for the three feeding types. However, the greater daily intake of calcium by the formula-fed infants (327 mg [8.2 mmol], 464 mg [11.6 mmol], and 652 mg [16.3 mmol] for human milk, cow milk, and soy milk infants, respectively) led to net calcium retention that was very similar among the three feeding types, with slightly higher values for the formula-fed infants. The bioavailability of minerals from protein hydrolysate formulas may be lower than from human milk, as indicated in studies in humans (Rigo et al., 1995) as well as in infant rhesus monkeys (Rudloff and Lonnerdal, 1990). However, since these studies were performed using a greater total intake of calcium from infant formulas compared with human milk, it is difficult to interpret the dietary bioavailability.

Numerous studies have compared whole body or regional bone mineral accretion in infants fed human milk, cow milk formula, or soy formula (Chan et al., 1987; Greer et al., 1982b; Hillman et al., 1988; Mimouni et al., 1993; Pittard et al., 1990; Specker et al., 1997; Steichen and Tsang, 1987). Results have varied, but there appears to be a greater bone mineral accretion in cow milk formula-fed infants compared with those fed human milk or soy formula. In spite of this trend, there is no evidence that this difference is beneficial or clinically significant.

No published studies indicate that increasing bone accretion using high calcium-containing formulas or cow milk during infancy leads to greater bone mineralization in later childhood or adolescence. In contrast, Bishop et al. (1996) suggested that premature infants fed human milk in early neonatal life, as opposed to cow milk formula with greater mineral content, may have greater BMC at 5 years of age. This finding is supported by a study in dogs suggesting that in forming stable bone, low calcium intakes early in life might be preferred to greater intakes (Gershoff et al., 1958). These findings need to be replicated to determine whether this effect is relevant to full-term infants. The possibility that "programming" of infants such that lower intakes and retention of calcium is beneficial to long-term mineralization is therefore possible but unproven. Further research is needed to define the risks and possible benefits of high calcium intakes during infancy.

Assuming an efficiency of calcium absorption of 38 percent from cow milk-based formula (Fomon and Nelson, 1993) with a calcium content approximately 50 percent higher than that from human

milk, then a net calcium retention will be achieved that is at least comparable to that of the human milk-fed infant. Based on an average intake from human milk of 210 mg (5.3 mmol)/day, intakes of 315 mg (7.9 mmol)/day from formula should be adequate for infants 0 through 6 months of age. For infants ages 7 through 12 months, based on an average intake from human milk of 130 mg (3.2 mmol)/day, 195 mg (4.8 mmol)/day should be obtained from formula. When added to the average intake of calcium (by formula-fed infants) from solid food of 140 mg (3.5 mmol)/day, an intake of 335 mg (8.3 mmol)/day is adequate for infants ages 7 through 12 months who are fed formula and solid foods.

It is difficult to accurately estimate the calcium intake needed for infants fed the various special formulas, including soy protein-based and protein hydrolysate formulas. However, based on the data of Rigo et al. (1995) and Fomon and Nelson (1993), an additional 20 percent above the 315 mg (7.9 mmol) calculated above should be sufficient to compensate for decreased bioavailabilty from those sources. This added amount is likely to result in a net calcium retention comparable to that of infants fed formula with higher calcium concentrations.

Hypocalcemia. Hypocalcemia is a relatively common neonatal problem (Salle et al., 1990). However, this condition requires special evaluation, which is beyond the scope of an evaluation of the AI for calcium for a healthy population of infants.

Ages 1 through 3 and 4 through 8 Years

Indicators Used to Set the AI

Balance Studies. Much of the available data from balance studies of young children, which were principally conducted prior to 1960, have been compiled and reviewed (Matkovic, 1991; Matkovic and Heaney, 1992). In 2- to 8-year-old children, mean calcium intakes (± SD) of 821 ± 63 mg (20.5 ± 1.5 mmol)/day led to calcium retentions of 174 ± 81 mg (4.3 ± 2.0 mmol)/day (about 21 percent of intake).

A recent study used stable isotopes to estimate calcium retention from milk in girls 5 to 12 years of age (Abrams and Stuff, 1994). Calcium intake based on 3-day dietary records was 907 ± 188 mg (22.7 ± 4.7 mmol)/day, urinary calcium excretion was 78 ± 48 mg (2.0 ± 1.2 mmol)/day, and mean absorption fraction was 28 ± 8 percent. Using estimated values for endogenous fecal calcium excretion of 1.4 ± 0.4 mg/kg/day (Abrams et al., 1991), their calculated

calcium retention was 130 mg (3.3 mmol)/day, a value somewhat lower than the 174 mg (4.3 mmol)/day obtained in the meta-analyses cited above (Matkovic, 1991; Matkovic and Heaney, 1992).

Although calcium balance with varying levels of intake is possibly a more useful method, few investigators have estimated it in children. Calcium retention averaged 76 mg (1.9 mmol)/day in five girls aged 3 to 5 years when the girls had an intake of 370 mg (9.3 mmol)/day for 8 weeks and increased to an average of 122 mg (3.0 mmol)/day when the girls consumed 615 mg (15.4 mmol)/day for the next 5 weeks (Outhouse et al., 1939). Calcium intakes of about 200 to 280 mg (5 to 7 mmol)/day in children from India resulted in absorption rates of approximately 50 percent of the calcium while maintaining a small positive balance of 50 to 60 mg (1.3 to 1.5 mmol)/day (Begum and Pereira, 1969).

Calcium Accretion. The few studies of usual calcium accretion rates in small children give generally comparable results to that derived from balance studies. Calcium accretion rate was estimated from body weight values during childhood and adolescence (Leitch and Aitken, 1959). Although the method was not independently validated, there is a very close correlation between BMC and body weight in small children (Ellis et al., 1996). Calcium accretion on the order of 60 to 100 mg (1.5 to 2.5 mmol)/day by boys and girls aged 2 to 5 years and 100 to 160 mg (2.5 to 4.0 mmol)/day by boys and girls aged 6 to 8 years was calculated.

Bone Mineral Content. Recently, total body BMC by DXA was used to calculate average mineral increments in a population of approximately 100 children aged 3 to 10 years (Ellis et al., 1997). The rate of accretion in Caucasian ($n = 46$) and Hispanic ($n = 23$) children increased from approximately 150 mg (3.8 mmol)/day of calcium at age 5 to approximately 200 mg (5 mmol)/day at age 8. Values for African Americans ($n = 36$) were approximately 20 to 30 mg (0.5 to 0.8 mmol)/day greater at each age.

Intervention trials in which children were randomized to different calcium intakes have resulted in short-term changes in BMC. In one of the few intervention trials conducted in young children, 22 prepubertal identical twin pairs averaging 7 years of age were randomized to receive either calcium supplements or placebo (Johnston et al., 1992). Those receiving supplements had an increase in their mean intake from approximately 900 to 1,600 mg (22.5 to 40 mmol)/day which resulted in a significant increase in BMD in the radius and lumbar spine after 36 months of treatment

compared to the control twins. However, the increase in BMD was not sustained in a long-term follow-up study when those receiving supplements returned to their normal diets (Slemenda et al., 1997).

In another intervention study, 162 Chinese children who were 7 years of age with low daily calcium intakes (average 280 mg [7 mmol]) were randomly assigned to receive 300 mg (7.5 mmol)/day of a calcium supplement or placebo (Lee et al., 1994). After 18 months, the supplemented group had a significantly greater gain in BMC at the midshaft radius. In a follow-up study for another 18 months, the benefits of calcium supplementation disappeared after the supplements were withdrawn (Lee et al., 1996). In a similar study, greater increases in lumbar spine BMC were seen in 7-year-old children from Hong Kong with average calcium intakes of 570 mg (14.3 mmol)/day who were randomized to receive 300 mg (7.5 mmol)/day supplement compared with those who received a placebo (Lee et al., 1995).

Taken together, the above studies suggest that further evidence is needed regarding the length of time and level of supplementation necessary before a precise requirement value can be based on supplementation data in prepubertal children. There are no long-term studies in which the effects of supplemental calcium given to children prior to age 9 have been evaluated during adulthood.

AI Summary: Ages 1 through 3 and 4 through 8 Years

For females aged 1 through 8 years, calcium accretion in the range of 60 to 200 mg (1.5 to 5 mmol)/day has been predicted from both indirect estimates based on body weight (Leitch and Aitken, 1959) and direct estimates of bone mineral content using DXA (Ellis et al., 1997). The precise calcium intake needed to achieve such calcium accretion cannot be obtained from available data. From balance studies in the older age group, a calcium intake of 800 to 900 mg (20 to 22.5 mmol)/day would result in mean calcium retention up to 174 mg/day. Thus, for the 4- through 8-year-old age group, the AI for calcium is 800 mg (20 mmol)/day. As there are no balance studies available in boys, the data for girls has to be applied to both sexes.

The primary balance data described above for 4- through 8 year olds do not include adequate data applicable to younger children in the second and third years of life. Therefore, AIs for this period must be estimated from data for other age groups. Net accretion appears to be approximately 100 mg (2.5 mmol)/day during this life stage (Leitch and Aitken, 1959). Therefore, using an estimate

of 20 percent net calcium retention in children based on the data from 4 through 8 year olds (Matkovic, 1991; Matkovic and Heaney, 1992), it is reasonable to set the AI for calcium at 500 mg (12.5 mmol)/day intake to achieve the 100 mg (2.5 mmol)/day retention. For this age group, there is a substantial need for further investigation using both balance techniques and bone densitometry to more precisely estimate calcium needs.

AI for Children	**1 through 3 years**	**500 mg (12.5 mmol)/day**
	4 through 8 years	**800 mg (20.0 mmol)/day**

Utilizing the 1994 CSFII data, adjusted for day-to-day variation (Nusser et al., 1996), the median calcium intake is 766 (19.2 mmol)/day for children aged 1 through 3 years (see Appendix D). Their AI of 500 mg (12.5 mmol)/day will fall between the tenth percentile (468 mg [11.7 mmol]/day) and the twenty-fifth percentile of calcium intake (599 mg [15 mmol]/day). For children aged 4 through 8 years, the median calcium intake is 808 mg (20.2 mmol)/day, which is very close to the AI of 800 mg (20 mmol)/day for this age group.

Special Considerations

Chronic Illness. Many chronic illnesses that affect children are associated with abnormalities of calcium metabolism and bone mineralization. Among the most significant of these are juvenile rheumatologic conditions (Reed et al., 1990), renal disease (Stapleton, 1994), liver failure (Bucuvalas et al., 1990), and endocrine disturbances, including insulin-dependent diabetes mellitus (Favus and Christakos, 1996). The value of adjustments in calcium intake for children with these conditions is beyond the scope of this report.

Ages 9 through 13 and 14 through 18 Years

Sexual Maturity

From 9 through 18 years of age, calcium retention increases to a peak and then declines. The peak calcium accretion rate typically occurs at mean age 13 years for girls and 14.5 years for boys (Martin et al., 1997). After menarche, calcium retention in girls declines rapidly (Weaver et al., 1995) as does bone formation and bone resorption (Abrams et al., 1996b; Wastney et al., 1996). Even though bone formation and resorption decrease exponentially after me-

narche, calcium intakes required to achieve desirable retention do not necessarily fall because calcium absorption efficiency decreases. This menarcheal change in absorption was not observed in African American girls (Abrams and Stuff, 1994). Measures of sexual maturity are better predictors of calcium retention than is chronological age during this developmental period.

In a cross-sectional evaluation in 136 males and 130 females aged 4 to 27 years, BMD of total body, lumbar spine, and femoral neck increased significantly with age until 17.5 years in males and 15.8 years in females (Lu et al., 1994). The later timing of peak BMD in boys may relate in part to the fact that BMD is more strongly correlated with weight than with age (Ponder et al., 1990; Teegarden et al., 1995).

Indicators Used to Set the AI

Calcium Retention. The desirable level of calcium retention for children in this age group was based upon new information on whole body bone mineral accretion for 228 children followed over 4 years between the ages of 9 and 19 years (Martin et al., 1997). The average peak velocity of bone mineral content which occurs between the ages 9.5 to 19.5 years was 320 g/year in boys and 240 g/year in girls. Using the assumption that bone mineral is 32.3 percent calcium, these values correspond to a daily calcium retention of 282 mg (7.1 mmol) in boys and 212 mg (5.3 mmol) in girls. One limitation of these data is that they do not provide information as to whether peak bone mineral accretion would be greater at higher calcium intakes than that consumed by the children studied; the mean intake for boys was 1,045 mg (26 mmol)/day at ages 10 to 12 years and 1,299 mg (32.5 mmol)/day at ages 13 to 15 years while for girls it was 903 mg (22.5 mmol)/day at 10 to 12 years and 954 mg (23.8 mmol)/day at ages 13 to 15 years (Martin et al., 1997). However, because the intakes of the children in the study were based on 24-hour recall data over 4 years, they are subject to under-reporting as previously observed (Livingstone et al., 1992), so actual intakes may have been higher.

In order to derive an estimate of calcium intake which would allow for the level of accretion of calcium in bone as derived above, a model for describing the relationship between calcium intake and retention was adopted. It had been applied to one set of calcium balance studies in girls (Jackman et al., 1997) (the method is described in detail in Appendix E).

The majority of the balance studies to which the model was ap-

plied are for girls aged 11 through 14 years, and all data are from Caucasians. For this report the nonlinear regression equation was derived by combining the optimally designed calcium balance studies of Jackman et al. (1997), Matkovic et al. (1990), and Greger et al. (1978) which represented 80 children aged 12 through 15 years. The measurements were made over the last 2 weeks of a 3-week balance study in girls consuming calcium intakes of 823 to 2,164 mg (20.6 to 54.1 mmol)/day. The retention of calcium was not corrected for sweat or skins losses of calcium in these studies.

The non-linear regression equation was solved to determine the calcium intake required to achieve a desirable retention of calcium of 282 mg (7.1 mmol)/day for boys and 212 mg (5.3 mmol)/day for girls based on peak whole body bone mineral accretion during adolescence (Figure E-1). The value used for sweat losses of 55 mg (1.4 mmol)/day (Peacock, 1991) was added to the desired retention value since these losses had not been accounted for in the calcium retention studies. The estimate of calcium intake that would result in a desirable level of retention was 1,070 mg (26.8 mmol)/day for females and 1,310 mg (32.8 mmol)/day for males. At this time there are insufficient data to subdivide the age range of 9 through 18 years for either bone mineral accretion or balance measures.

The approach used in this review results in a value which is midway between two other estimates of the calcium intake necessary to achieve a plateau balance. In applying a two-component split, linear regression model to balance studies published between 1922 and 1992, Matkovic and Heaney (1992) identified a plateau calcium intake of approximately 1,480 mg (37 mmol)/day during growth. Using the nonlinear regression model (Jackman et al., 1997) on the same data set of reported balances as was used by Matkovic and Heaney (1992) resulted in a lower plateau estimate of 820 mg (20.5 mmol)/day of calcium. It should be noted that included in this historical data set were balances which were measured in children who were not yet equilibrated to the study intake. For the analysis conducted for this report, data were included from published studies only if an adaptation period of at least 2 weeks had occurred before the balance period. Thus, the current recommendation is thought to be a more rigorous analysis of the data available.

Clinical Trials Measuring Bone Mineral Content. Several randomized trials have been conducted in children through adolescence which provide evidence that increasing dietary intakes of calcium of girls above their habitual intake of about 900 mg (22.5 mmol)/day is

associated with positive effects on bone mineral accretion, especially during the pre-pubertal stage (Table 4-2). In the Lloyd et al. (1993) study, girls with a mean age of 11.9 years were supplemented (total daily intake of 1,370 ± 303 mg [34.2 ± 7.6 mmol]) and compared with a placebo group (total daily intake 935 ± 258 mg [23.4 ± 6.4 mmol]). After 18 months of supplementation, the girls had greater increases in lumbar spine BMD (18.7 versus 15.8 percent), lumbar spine BMC (39.4 versus 34.7 percent), and total body BMD (9.6 versus 8.3 percent). In the Chan et al. (1995) study, the girls (mean age 11 years) supplemented for 12 months (total daily intake 1,437 ± 366 mg [35.9 ± 9.2 mmol]) had significantly greater increases in lumbar spine BMD (22.8 ± 6.9 versus 12.9 ± 8.3 percent) and total body BMC (14.2 ± 7.0 versus 7.6 ± 6.0 percent) than control subjects (total daily intake 728 ± 321 mg [18.2 ± 8.0 mmol]). In a third study (Johnston et al., 1992), identical twins, aged 6 to 14 years, were given a supplement (total daily intake approximately 1,600 mg [40 mmol]) or a placebo (daily intake 900 mg [22.5 mmol]). When examined by pubertal status, the prepubertal twins (22 pairs) had a greater bone response to calcium supplementation than did the pubertal twins (23 pairs). The pubertal subjects in this study showed no significant effect of supplementation, unlike the pubertal girls in both the Lloyd et al. (1993) and Chan et al. (1995) studies.

Mounting evidence from randomized clinical trials suggests that the bone mass gained during childhood and adolescence through calcium or milk supplementation is not retained postintervention (Fehily et al., 1992; Lee et al., 1996; Slemenda et al., 1997). Upon cessation of the intervention, the component of calcium's effect due to reduction of the remodeling space disappears, as the space expands again. Further research is required to determine the long-term effects of higher calcium intakes during adolescence and the specific effect of calcium intake on bone modeling and achievement of genetically programmed peak bone mass.

Factorial Approach. For children ages 9 through 18 a more traditional factorial approach for estimating calcium requirements is to sum calcium needs for growth (accretion) plus calcium losses (urine, feces, and sweat) and adjust for absorption. Using this method, estimates for calcium requirements for adolescent girls and boys are 1,276 and 1,505 mg (31.9 and 37.6 mmol)/day, respectively (Table 4-3). Calcium accretion estimates, based on whole body bone mineral mass measurements by DXA, were obtained from a 4-year prospective study in 228 children aged 9.5 to 19.5 years (Mar-

TABLE 4-2 Differences in Mean Changes in Bone Mineral Content and Bone Mineral Density in Calcium Treated vs. Placebo Groups in Randomized, Controlled Trials in Adolescents

Source	No.	Age (y)	Sex	Length Study (mo)	Calcium Intake Controls (mg/day)	Calcium Intake Treatment (mg/day)	Site	Group Mean Differences	
								BMC (g)	Change in BMD (%)
Chan et al., 1995	48	9–13	female	12	728	1,437	Total body	35.52	
Johnston et al., 1992	140	6–14	female and male	36	908	1,612	Midshaft radius		2.5
							Distal radius		3.3
							Lumbar spine		0.7
							Femoral neck		0.4
							Ward's triangle		1.2
							Greater trochanter		1.8
Lloyd et al., 1993	94	11.9 ± 0.5	female	18	960	1,314	Total body	13.32	

TABLE 4-3 Factorial Approach for Determining Calcium Requirements During Peak Calcium Accretion in White Adolescents

	Number of Observations	Females (mg/day)	Number of Observations	Males (mg/day)
Peak calcium accretion	507	212[a]	471	282[a]
Urinary losses	28	106[b]	14	127[c]
Endogenous fecal calcium	14	112[d]	3	108[e]
Sweat losses		55[f]		55[f]
Total		485		572
Absorption, percent	14	38[d]	14	38[d]
As adjusted for absorption		1,276		1,505

[a] Martin et al., 1997, using peak bone mineral content velocity.
[b] Weaver et al., 1995 and Greger et al., 1978.
[c] Matkovic, 1991.
[d] Wastney et al., 1996 for mean age 13 years on calcium intakes of 1,330 mg/day.
[e] Abrams et al., 1992.
[f] Taken from Peacock (1991) who adjusted the adult data of Charles et al. (1983) for body weight.

tin et al., 1997). The mean fractional absorption value of 38 percent was based on a study of girls, aged 13 ± 1 years, who consumed an average of 1,330 mg (33.3 mmol)/day of calcium (Wastney et al., 1996). It is unknown whether there are gender differences in absorption in this age range. The values for endogenous excretion and absorption in males in Table 4-3 are based on very few data points, and the values for sweat losses are extrapolated from adult data. Variability about these estimates is large. The values derived from the factorial approach are slightly higher than those obtained using the calcium retention model, but fall within the range of these values and those derived from the clinical trials described above. Because of the extrapolation of values from studies in girls to boys and from adults used in this approach, it was deemed inappropriate to use these values as a basis for an EAR.

Epidemiological Evidence. Several cross-sectional studies have identified a positive association between calcium consumption and bone density in children (Chan, 1991; Ruiz et al., 1995; Sentipal et al., 1991), whereas others have found no such association (Grimston et al., 1992; Katzman et al., 1991; Kröger et al., 1992, 1993). The studies showing the positive association tended to include a significant proportion of study subjects with low calcium intakes. A study

of French children (Ruiz et al., 1995) found that 93 percent of the children with low vertebral BMD and 84 percent of those with low femoral neck BMD had dietary calcium intakes below 1,000 mg (25 mmol)/day; the investigators concluded that dietary calcium requirements for prepubertal and pubertal children were above 1,000 mg (25 mmol)/day.

Several retrospective studies suggest that higher calcium intakes in childhood are associated with greater bone mass in adulthood (Halioua and Anderson, 1989; Matkovic et al., 1994; Nieves et al., 1995; Sandler et al., 1985). As it appears now, and pending further research in this area, higher calcium intakes likely need to be maintained throughout growth in order to produce a higher peak bone mass.

AI Summary: Ages 9 through 13 and 14 through 18 Years

The three major lines of evidence for calcium needs in this age group—the factorial approach, calcium retention to meet peak bone mineral accretion, and clinical trials in which bone mineral content was measured in response to variable calcium intakes—provide estimates of calcium intake in the range of 1,100 to 1,600 mg (27.5 to 40 mmol)/day to attain a desirable level of calcium retention. Most of the data are based on balance studies and clinical intervention trials in girls. Thus, it is important to note that the value of peak bone mineral accretion for boys had to be used in the equation derived from balance studies in girls due to lack of data on boys. Given the extrapolation to boys for the balance data, the clinical trials being conducted primarily in girls, and the lack of data on bone mineral accretion at higher calcium intakes than that reported by Martin et al. (1997), it was inappropriate to establish a gender-specific AI for this age group. In considering collectively the evidence above, an AI of 1,300 mg (32.5 mmol)/day was judged as a reasonable goal for calcium intake for both boys and girls in this age group. Too few data exist in males to allow a gender difference to be established or to recommend different intakes within the age range.

AI for Boys	**9 through 13 years**	**1,300 mg (32.5 mmol)/day**
	14 through 18 years	**1,300 mg (32.5 mmol)/day**
AI for Girls	**9 through 13 years**	**1,300 mg (32.5 mmol)/day**
	14 through 18 years	**1,300 mg (32.5 mmol)/day**

Utilizing the 1994 CFSII data, adjusted for day-to-day variation

(Nusser et al., 1996), the median calcium intake for boys aged 9 through 13 is 980 mg (24.5 mmol)/day, the seventy-fifth percentile of intake is 1,245 mg (31.1 mmol)/day and the ninetieth percentile of intake is 1,520 mg (38 mmol)/day (see Appendix D). Thus, the AI for boys ages 9 through 13 years of 1,300 mg (32.5 mmol)/day is slightly above the seventy-fifth percentile of calcium intake. For girls in this age range, the median calcium intake is 889 mg (22.2 mmol)/day, and the ninetieth percentile of intake is 1,313 mg (32.8 mmol)/day. Thus, the AI for girls ages 9 through 13 years of 1,300 mg (32.5 mmol)/day, is slightly below the ninetieth percentile of calcium intake based on the 1994 CSFII data.

For boys aged 14 through 18 years, the median calcium intake is 1,094 mg (27.4 mmol)/day, and the seventy-fifth percentile is 1,422 mg (35.6 mmol)/day. Thus, for boys ages 14 through 18 years, the AI for calcium of 1,300 mg (32.5 mmol)/day would fall between the median and seventy-fifth percentiles of intake. For girls in this age range, the median calcium intake was 713 mg (17.8 mmol)/day, and the ninetieth percentile was 1,293 mg (32.3 mmol)/day. Thus, for girls ages 14 through 18 years, the AI for calcium of 1,300 mg (32.5 mmol)/day would be close to the ninety-fifth percentile of intake based on the 1994 CSFII data.

Ages 19 through 30 Years

Peak Bone Mass

During the age span of 19 through 30 years, peak bone mass is achieved. Growth of long bones has ceased, but consolidation of bone mass continues. The age at which peak mass is achieved appears to vary with the skeletal site. Using single measures of BMC by DXA on 247 females aged 11 to 32 years, 92 percent of the total body bone mass observed was present by age 17.9 years and 99 percent by age 26.2 years (Teegarden et al., 1995). In a cross-sectional study of 265 Caucasian females, only a 4 percent additional increase in total skeletal mass from age 18 to 50 years was reported (Matkovic et al., 1994). In a longitudinal study (with up to 5-year follow-up) of 156 women aged 18.5 to 26 years at entry and with a mean daily calcium intake from food and supplements of 786 mg (19.7 mmol), total body BMC increased by an average of 1.2 percent per year during the third decade of life, although within that age decade, the rate of gain slowed with age (Recker et al., 1992).

With regard to individual skeletal sites, no difference in subjects'

BMC at several sites was detected after the age of 18 except for the skull, which continued to gain mass (Matkovic et al., 1994). In a longitudinal study (Recker et al., 1992), lumbar BMC increased by a median gain of 5.9 percent, and the forearm increased by 4.8 percent during the third decade of life. In a smaller study of 45 females aged 9 to 21 years, BMC of the whole body, spine, and femoral neck plateaued at age 16 years (Katzman et al., 1991). Bone density of the hip decreased after age 17 years (Matkovic et al., 1994; Theintz et al., 1992). In summary, the age of peak bone mass appears to vary with skeletal site and sex. Nevertheless, taken all together, the data indicate that the skeleton continues to accrete mass for approximately 10 years after adult stature is achieved.

Indicators Used to Set the AI

Calcium Retention. A desirable level of calcium retention (the level of positive calcium balance) for the 19- to 30-year age group was set as the retention of calcium equivalent to the reported calcium accretion derived from studies of bone mineral accretion during the third decade (Peacock, 1991). The limitation of these data is that they were derived from metacarpal morphometry data (Garn, 1972). To date, there are no data on whole body bone mineral accretion using DXA technology nor for groups of subjects consuming variable amounts of dietary calcium. The accretion of calcium based on these data was 10 mg (0.25 mmol)/day for females and 50 mg (1.3 mmol)/day for males. This large discrepancy in calcium accretion between genders may reflect the older age at which males achieve peak bone mineral content velocity (Martin et al., 1997) or inaccuracies in the older bone densitometry methods.

The relationship between calcium intake and retention for this age group was computed from a compilation of balance studies in 163 young adults (26 males and 137 females), aged 18 to 30 years, from the literature between 1922 and 1992 as compiled by Matkovic and Heaney (1992). The non-linear regression approach of Jackman et al. (1997) was applied to these data (Appendix E) and the regression equation solved to determine the calcium intake at which a desirable daily calcium retention of 50 mg (1.3 mmol)/day for males and 10 mg (0.3 mmol)/day for females could be achieved. A value for sweat losses of 63 mg (1.6 mmol)/day (Charles et al., 1983) was added to the level of desired retention since these losses had not been corrected for in the calcium balance studies. The estimated calcium intake at which a desirable retention would be

TABLE 4-4 Factorial Approach for Determining Calcium Requirements in Adults Aged 19 through 30 Years

	Females (mg/day)	Males (mg/day)
Peak calcium accretion	10[a]	50[a]
Urinary losses	203[b]	162[e]
Endogenous fecal calcium	132[b]	156[f]
Sweat losses	63[c]	63[c]
Total	408	431
Absorption, percent	30[d]	30[d]
As adjusted for absorption	1,360	1,437

[a] Taken from calculations by Peacock (1991) based on metacarpal morphometry data of Garn (1972).
[b] Wastney et al. (1996).
[c] Charles et al. (1983).
[d] Heaney et al. (1988).
[e] Matkovic (1991).
[f] Heaney and Skillman (1964).

achieved was 1,026 mg (25.6 mmol)/day for females and 1,236 mg (30.9 mmol)/day for males (Figure E-2).

Using the same database with data from men and women combined to determine the plateau intake using the two-component split, linear-regression model of Matkovic and Heaney (1992), the plateau retention of calcium was reached at an intake of 957 mg (23.9 mmol)/day.

Factorial Approach. The factorial approach for estimating calcium requirements for young adults is given in Table 4-4. This approach gives higher daily estimates of requirements (1,360 mg [34 mmol] for females and 1,437 mg [35.9 mmol] for males) than the desirable calcium retention approach (see above). The differences in derived values for calcium intake may be a result of the correction for endogenous fecal calcium applied in the factorial method which is based on only one recent study (Wastney et al., 1996) and/or the fact that a 30 percent absorption factor was applied. For the latter, the absorption value is taken from a derivative report which included multiple study designs on 16 women and 6 men (Heaney et al., 1988), and thus represents the average of all the subjects. Given the variety of study designs, it isn't possible to apply the gender-specific data.

AI Summary: Ages 19 through 30 Years

For this age group, estimates of average calcium requirements

were hindered because of no reported randomized clinical trials testing multiple intakes of calcium, the lack of data on whole body bone mineral accretion, and the uncertainties in the values for endogenous fecal and sweat losses of calcium used in the factorial model. Thus, the estimate for the AI relies on using available calcium balance studies to determine intakes at which small gains in bone mineral content can be achieved. Because of the uncertainties related to the five-fold difference in estimated bone calcium accretion between genders during this time period, and the fact that the balance data are predominantly from women, the estimate of calcium intake from the calcium retention analysis for women was adopted for both genders. The estimate of an AI of 1,000 mg (25 mmol)/day was judged to be appropriate for this age group.

Based on desirable calcium retention data and with consideration of the estimates of calcium need from various methods, the AI requirement for both men and women ages 19 through 30 years is set at 1,000 mg (25 mmol)/day.

AI for Men	**19 through 30 years**	**1,000 mg (25 mmol)/day**
AI for Women	**19 through 30 years**	**1,000 mg (25 mmol)/day**

Adjusting the 1994 CSFII data for day-to-day variation (Nusser et al., 1996), the median calcium intake for men aged 19 through 30 years is 954 mg (23.9 mmol)/day (see Appendix D), which is fairly close to the AI of 1,000 mg (25 mmol)/day for this age group. For women in this age range, the median calcium intake is 612 mg (15.3 mmol)/day, while the ninetieth percentile of intake is 985 mg (24.6 mmol)/day. Thus, an AI of 1,000 mg (25 mmol)/day is slightly above the ninetieth percentile of calcium intake based on the 1994 CSFII data.

Ages 31 through 50 Years

Indicators Used to Set the AI

Calcium Retention. For this age group, as for the others, balance studies were examined to identify the intake associated with a desirable calcium retention—the plateau intake, that at which there is no net loss of calcium. Two balance studies are available that examined estrogen-replete women on their usual calcium intakes (Heaney et al., 1978; Ohlson et al., 1952). Calcium balance was estimated in 25 women aged 30 to 39, with a mean calcium intake of 950 ± 300 mg (23.7 ± 7.5 mmol)/day and 34 women aged 40 to

49, with a mean intake of 840 ± 292 mg (21 ± 7.3 mmol)/day (Ohlson et al., 1952). In each age group, calcium intake and balance were positively correlated ($r = 0.43$ and $r = 0.44$). Only six women in the younger group and eight in the older group consumed more than 1,000 mg (25 mmol)/day. In the second study (Heaney et al., 1978) of 130 premenopausal women, aged 35 to 50 with a mean calcium intake of 661 ± 328 mg (16.5 ± 8.2 mmol)/day, calcium intake and balance were positively correlated ($r = 0.26$). This study included very few women with intakes over 1,000 mg (25 mmol)/day. From these data, it is apparent that the plateau intake is not below 1,000 mg (25 mmol)/day. However, the intake associated with a desirable retention so that no net loss will occur cannot be identified without additional balance studies in women with calcium intakes greater than 1,000 mg (25 mmol)/day. Available balance data from a large study in men (Spencer et al., 1984), with the wide age range of 34 to 71 years will be considered under the age group of 51 through 70 years.

Bone Mineral Density. The two available intervention trials in women in this age range (Baran et al., 1990; Elders et al., 1994) support a plateau intake at or above 1,000 mg (25 mmol)/day. In 37 premenopausal women aged 30 to 42 years randomly assigned to either their usual calcium intakes of 810 ± 367 mg (20.5 ± 9.2 mmol)/day or increased dairy product consumption to a total intake of 1,572 ± 920 mg (39.3 ± 24 mmol)/day, the group consuming extra dairy products had significantly reduced vertebral BMD loss over 3 years (Baran et al., 1990). Similarly, calcium supplementation of 1,000 and 2,000 mg (25 and 50 mmol)/day in premenopausal women aged 46 and older with a usual mean calcium intake of 1,100 mg (27.5 mmol)/day significantly reduced vertebral bone loss (Elders et al., 1994). In this study, the higher total intake (3,100 mg [77.5 mmol]/day) was no more effective than the 2,100 mg (52.5 mmol)/day intake.

Factorial Approach. If the needs for calcium accretion that are described for the young adults aged 19 through 30 years are removed from Table 4-4, the AIs based on a factorial approach would be 1,360 mg (34 mmol)/day and 1,270 mg (31.7 mmol)/day for females and males, respectively. Endogenous fecal calcium losses for 191 women aged 35 to 59 years averaged 102 ± 25 mg (2.6 ± 0.6 mmol)/day (Heaney and Recker, 1994), which if substituted in Table 4-4 would not appreciably reduce the net total calcium need. As indicated earlier, these values must be considered in light of the

uncertainty of the values used for endogenous and sweat losses as well as efficiency of absorption.

AI Summary: Ages 31 through 50 Years

Based on available data from balance studies and BMD, the AI is placed at 1,000 mg (25 mmol)/day. Too few data for men are available to justify a separate AI for them.

AI for Men	**31 through 50 years**	**1,000 mg (25 mmol)/day**
AI for Women	**31 through 50 years**	**1,000 mg (25 mmol)/day**

Using the 1994 CSFII intake data, adjusted for day-to-day variation (Nusser et al., 1996), the median calcium intake for men, aged 31 through 50 years, is 857 mg (21.4 mmol)/day and their seventy-fifth percentile of intake is 1,112 mg (27.8 mmol)/day (see Appendix D). Their AI of 1,000 mg (25 mmol)/day falls between the median and seventy-fifth percentile of calcium intake. Median calcium intake for women in this age range is 606 mg (15.2 mmol)/day; their ninetieth percentile of intake is 961 mg (24 mmol)/day and their ninety-fifth percentile is 1,082 mg (27.1 mmol)/day. Thus, their AI of 1,000 mg (25 mmol)/day falls between the ninetieth and ninety-fifth percentile of calcium intake based on the 1994 CSFII data.

Ages 51 through 70 Years

Indicators Used to Set the AI for Men

Calcium Retention. Desirable retention of calcium in men aged 51 through 70 years is zero which assumes that no net positive accretion of bone at this age in replete individuals serves a functional advantage. The relationship between calcium intake and calcium retention was determined from 181 balance studies conducted in ambulatory males of mean age 54 years (range 34 to 71 years) (Spencer et al., 1984). The subjects could not be divided into different age categories based on the data reported. Six different calcium intake levels ranging from 234 to 2,320 mg (5.8 to 58 mmol)/day were studied. The distribution of intakes in the 181 balance studies were: 111 balance studies in subjects with daily calcium intakes below 1,200 mg (30 mmol), 22 at approximately 1,200 mg, and 48 at intakes above 1,200 mg. The nonlinear regression equation derived from these data (Appendix E) was solved for a desirable reten-

tion of zero balance plus 63 mg (1.6 mmol)/day of sweat loss (Charles et al., 1983) since the balance studies were not corrected for sweat losses. The estimated calcium intake at which this level of retention would be achieved is 995 mg (23.9 mmol)/day (Figure E-3). Thus, based on balance studies in men, a calcium intake to achieve the desired zero calcium retention is about 1,000 mg (25 mmol)/day.

Other investigators have contributed balance data in men. In long-term studies, Malm (1958) assessed balance in 39 men who had calcium intakes of 460 and 940 mg (11.5 and 23.5 mmol)/day. Balance was positively associated with calcium intake, but too few men were studied at high-enough calcium intakes to identify a plateau balance level. Although small sample sizes limit their usefulness in this context, older balance studies in males (Ackerman and Toro, 1953; Bogdonoff et al., 1953; Outhouse et al., 1941; Schwartz et al., 1964) indicate that a plateau retention of calcium would be achieved with a calcium intake of 1,000 to 1,200 mg (25 to 30 mmol)/day, which is similar to that derived using the desirable retention model based on the data of Spencer et al. (1984).

Bone Mineral Density. Only one randomized, controlled, calcium intervention study in men has been reported (Orwoll et al., 1990). In this 3-year study of 77 men aged 30 to 87 years (mean age 58 years) with a mean usual dietary calcium intake of 1,160 (29 mmol)/day, supplementation with an additional 1,000 mg (25 mmol)/day of calcium and 10 μg (400 IU) of vitamin D did not significantly reduce spinal or forearm bone loss. This finding, that increasing calcium intake above a mean intake of about 1,200 mg (30 mmol)/day did not reduce bone loss further, suggests that intakes less than or equal to 1,200 mg (30 mmol)/day are adequate to maximize maintenance of bone mass in this age group.

Indicators Used to Set the AI for Women

Calcium Retention. Women have been more widely studied regarding calcium retention because they are particularly prone to osteoporosis. Several balance studies are reported in postmenopausal women with mean calcium intakes under 1,000 mg (25 mmol)/day. In 61 women with varying degrees of osteoporosis and with calcium intakes ranging from 200 to 1,000 mg (5 to 25 mmol)/day, a positive linear correlation between calcium intake and balance was noted, and was similar in women with or without vertebral fractures

(Marshall et al., 1976). Calcium balance and usual calcium intake were positively correlated in 41 estrogen-deprived postmenopausal women with a mean usual calcium intake of 659 296 mg (16.5 ± 7.4 mmol)/day (Heaney and Recker, 1982; Heaney et al., 1977). In 76 women aged 50 to 85 years balance became more positive as calcium intake increased from 650 to 830 mg (16.2 to 20.7 mmol)/day (Ohlson et al., 1952). Only 10 women in that study had self-selected dietary calcium intakes over 1,000 mg (25 mmol)/day. Collectively, these studies consistently demonstrate that postmenopausal women with dietary calcium intakes under 1,000 mg (25 mmol)/day have less calcium loss when they increase their calcium intake.

Only two balance studies in postmenopausal women with average usual calcium intakes higher than 1,000 mg (25 mmol)/day were identified. Balance studies performed in 85 women with vertebral osteoporosis, aged 48 to 77 years, on a mean self-selected calcium intake of 1,116 mg (27.9 mmol)/day showed generally improved calcium balance in those subjects with higher calcium intakes (Hasling et al., 1990); very few subjects in this study had calcium intakes above 1,500 mg (37.5 mmol)/day. Calcium balance in 18 women and 7 men with osteoporosis (aged 26 to 70, mean 53 years) who consumed an average of 1,214 mg (30.3 mmol)/day of calcium was higher in those with higher calcium intakes (Selby, 1994). Notably, the men and women appeared to fit along the same regression line when intake was related to balance.

Several conclusions can be drawn from these balance studies. First, it is difficult to determine if the calcium intake needed for men over age 50 to minimize calcium loss is below 1,200 mg (30 mmol)/day as few studies have been done with intakes between 800 and 1,200 mg (20 and 30 mmol)/day. Second, available balance data indicate that the intake requirement of women over age 50 is at least 1,000 mg (25 mmol)/day and no evidence indicates that it differs substantially from that of similarly aged men. Finally, there are too few balance data at high calcium intakes to allow examination of subgroups, such as women in early menopause or subjects with and without fractures.

Bone Mineral Density. Many randomized, controlled, calcium intervention trials have been conducted in postmenopausal women. Several investigators have studied women within the first 5 years of menopause (designated as early postmenopausal), the period of most rapid bone loss (Aloia et al., 1994; Dawson-Hughes et al., 1990; Elders et al., 1991; Prince et al., 1995; Riis et al., 1987). Others have studied older or late postmenopausal women (Chevalley et al., 1994;

Dawson-Hughes et al., 1990; Reid et al., 1995). The main results of these studies are shown in Table 4-1. These studies reveal that the effectiveness of calcium varies by skeletal site, by menopausal age, and with the usual calcium intakes of the study subjects. Apart from the initial bone remodeling transient in year 1, added calcium offers little benefit in BMD at the spine. In contrast, calcium generally has more impact on BMD at the more cortical-rich proximal radius, femoral neck, and total body. Late postmenopausal women tend to be more responsive to supplemental calcium than early postmenopausal women. In addition, late postmenopausal women with very low calcium intakes generally gain more from calcium supplementation than do women with higher usual calcium intakes (Dawson-Hughes et al., 1990, Elders et al., 1994).

The positive impact of supplemental calcium on BMD in women with low-to-moderate usual mean calcium intakes is generally consistent with the observation that increasing calcium intake improves calcium balance. Trials involving women with the highest usual calcium intakes are more useful in this context, and they demonstrate that increasing calcium intake above 750 mg (18.7 mmol) (Reid et al., 1995), 800 mg (20 mmol) (Prince et al., 1995), or 1,000 mg (25 mmol) (Riis et al., 1987) reduces loss of bone mineral from cortical-rich skeletal sites. Since 80 percent of the skeleton is comprised of cortical bone, one would expect changes in cortical bone to parallel balance changes. Trials in women with even higher usual calcium intakes are needed to test the balance study estimate of 1,200 mg (30 mmol)/day.

AI Summary: Ages 51 through 70 years

The AI for men and women ages 51 through 70 is set at 1,200 mg (30 mmol)/day based primarily on the clinical trial data in women which demonstrated a positive reduction of bone loss with calcium intakes over 1,000 mg (25 mmol)/day. In addition, balance studies in women (Hasling et al., 1990) and women and men (Selby, 1994), showed that calcium intakes up to 1,500 mg (37.5 mmol)/day (mean intakes of 1,116 mg [27.9 mmol]/day and 1,214 mg [30.4 mmol]/day, for the cited studies, respectively), were associated with higher calcium retention. Although a value of about 1,000 mg (25 mmol)/day was derived from the calcium retention model using balance studies in men, there were no data for calcium intakes between 800 and 1,200 mg (20 and 30 mmol)/day. For the reported balance studies in women, a plateau calcium retention value could not be derived. The AI of 1,200 mg (30 mmol)/day was chosen for this age group assuming that their needs would be somewhat high-

er that the 19- through 30-year age group since calcium absorption is known to fall with advancing age.

AI for Men	**51 through 70 years**	**1,200 mg (30 mmol)/day**
AI for Women	**51 through 70 years**	**1,200 mg (30 mmol)/day**

Utilizing the 1994 CSFII data, adjusted for day-to-day variation (Nusser et al., 1996), the median intake for men aged 51 through 70 years is 708 mg (17.7 mmol)/day (see Appendix D). Their AI of 1,200 mg (30 mmol)/day falls between the ninetieth percentile of intake, 1,122 mg (28.1 mmol)/day, and the ninety-fifth percentile of calcium intake, 1,268 mg (31.7 mmol)/day. For women in this age range, the median calcium intake is 571 mg (14.3 mmol)/day. Their AI markedly exceeds the ninetieth percentile of calcium intake, 891 mg (22.3 mmol)/day.

Special Considerations

Estrogen Loss and Osteoporosis. Although diminished estrogen at menopause causes accelerated bone loss, estrogen deficiency-related bone loss cannot be prevented by increasing calcium intake (see earlier section "Factors Affecting the Calcium Requirement"). Estrogen does to some extent influence calcium absorption, but available evidence is not sufficient to support different AIs for women in this age range depending on their menopausal status or their use of hormone replacement therapy.

Ages > 70 Years

Indicators Used to Set the AI

Calcium Retention. Few men over age 70 have participated in balance studies. In the studies in which they have been included, it is not possible to separate their data from those of the younger men studied. Among women, there are too few balance data at high calcium intakes to identify a plateau intake value. To the extent that the age-related decline in calcium absorption efficiency is not offset by increased renal conservation of calcium, the intake requirement for men and women would be expected to increase with advancing age.

Fracture Rates. Several intervention studies have revealed a linkage between calcium intake and the clinically important outcome, frac-

tures. In a large randomized trial in over 3,000 elderly retirement home residents (mean age 84 years), daily supplementation with 1,200 mg (30 mmol) of calcium and 20 μg (800 IU) of vitamin D reduced hip fracture and other nonvertebral fracture rates (Chapuy et al., 1992). In a randomized trial in younger men and women (aged 65 and older, mean age 71 years) residing at home, supplementation with 500 mg (12.5 mmol) of elemental calcium and 8.8 μg (352 IU) of vitamin D significantly reduced nonvertebral fracture rates (Dawson-Hughes et al., 1997). Notably, the men and women in this study had estimated usual dietary calcium and vitamin D intakes of 750 mg (18.8 mmol) and 5.0 μg (200 IU), respectively. Two other studies have assessed the effect of calcium alone on fracture rates (Chevalley et al., 1994; Recker et al., 1996). Among women with low usual daily calcium intakes (mean 450 mg [11.3 mmol]), calcium supplementation (1,200 mg [30 mmol]/day) reduced the vertebral fracture rate in women with prior vertebral fractures, but it did not reduce the risk of first vertebral fractures (Recker et al., 1996). In contrast, a reduction in first vertebral fractures with calcium supplementation of 800 mg (20 mmol)/day has been noted (Chevalley et al., 1994). Although these studies point to a favorable effect of calcium, additional studies are needed to estimate the magnitude of the impact of calcium intake on fracture rates. Available data do not allow use of fracture outcomes to identify the AI for calcium.

Bone Mineral Density. The randomized longitudinal trials (summarized in Table 4-5) that examined the effect of supplemental calcium (with or without vitamin D) on fracture incidence also assessed changes in BMD (Chapuy et al., 1992; Chevalley et al., 1994; Dawson-Hughes et al., 1997) or BMC (Recker et al., 1996). In each of these studies, there was a significant positive effect of calcium at one or more skeletal sites including the proximal femur (Chapuy et al., 1992; Dawson-Hughes et al., 1997), femoral shaft (Chevalley et al., 1994), spine (Dawson-Hughes et al., 1997), forearm (in women with prevalent vertebral fractures [Recker et al., 1996]), and total body (Dawson-Hughes et al., 1997).

AI Summary: Ages > 70 Years

Because there are too few data in men and women at high calcium intakes to allow estimation of the plateau intake, the AI is the same as that for 51 through 70 year olds—1,200 mg (30 mmol)/day.

AI for Men	**> 70 years**	**1,200 mg (30 mmol)/day**
AI for Women	**> 70 years**	**1,200 mg (30 mmol)/day**

Utilizing the 1994 CSFII intake data, adjusted for day-to-day variation (Nusser et al., 1996), the median calcium intake for men aged > 70 years is 702 mg (17.6 mmol)/day, and the ninety-fifth percentile of intake is 1,185 mg (29.6 mmol)/day (see Appendix D). Thus, the ninety-fifth percentile of calcium intake is very close to the AI of 1,200 mg (30 mmol)/day. For women in this age range, the median calcium intake is 517 mg (12.9 mmol)/day and the ninety-ninth percentile of intake is 1,037 mg (25.9 mmol)/day. Thus, nearly all women ages > 70 years are consuming less calcium than the AI.

Summary of Approaches Used for Adolescents and Adults

Desirable rates of calcium retention, determined from balance studies, factorial estimates of requirements, and limited data on BMD and BMC changes, have been used as the primary indicators of adequacy (Table 4-5). These indicators were chosen as reasonable surrogate markers to reflect changes in skeletal calcium content. In general, the decision to set AIs for calcium rather than EARs was based on the uncertainties in the these methods as discussed earlier, and the disparity between the estimates derived from these approaches and the limited observational data on calcium intakes of groups within the U.S. and Canadian populations.

Pregnancy

During pregnancy, approximately 25 to 30 g (625 to 750 mmol) of calcium are transferred to the fetus, with the majority of this transfer occurring during the third trimester (IOM, 1990). The major physiological adaptation of the mother to meet this increased calcium requirement is increased efficiency in intestinal absorption of calcium.

Both total and "free" (calculated as the molar ratio of $1,25(OH)_2D$ and vitamin D binding protein) serum $1,25(OH)_2D$ concentrations increase during pregnancy (Bouillon et al., 1981; Cross et al., 1995a; Kumar et al., 1979; Pitkin et al., 1979; Seki et al., 1991; Wilson et al., 1990) and may be responsible for the increase in calcium absorption that has been observed (Cross et al., 1995a; Heaney and Skillman, 1971; Kent et al., 1991). Whether the increase in $1,25(OH)_2D$ concentrations is a result of placental production or increases in serum PTH that may occur late in pregnancy (Pitkin et al., 1979) is

TABLE 4-5 Summary of Estimates of Calcium Needs Using Three Different Approaches

Age (y)	Desirable Retention (mg Ca/d)[a]	FactorialMethod (mg Ca/d)[b]
1–3	M/F - 100	M/F - 500
4–8	M/F - 200	No data
9–13 & 14–18	M - 282 (+55)	M - 1,505
	F - 212 (+55)	F - 1,276
19–30	M - 50 (+63)	M - 1,437
	F - 10 (+63)	F - 1,393
31–50	M - 0 (+0)	M - 1,270
	F - 0 (+102)	F - 1,360
51–70	M - 0 (+63)	M - 1,380
	F - 0 (+0)	F - 1,383
> 70	No data	No data

[a] Additional amount added to account for sweat losses given in parentheses.

[b] The factorial estimate was based on accretion values derived from measures of bone mineral content and the assumption that bone contains 32.3% calcium by weight (see text for details).

[c] The calcium retention model was based on balance studies from which the absolute intake and retention of individual subjects was modeled using non-linear regression analysis (Jackman et al., 1997). The derived equations were then solved to obtain an

Calcium Retention Model (mg Ca/d)[c]	Clinical Trials[d]
No data	No data
Calcium intake of 800–900 gave retention of +174	Calcium intakes (mg/d) of 600 vs. 300 (Lee et al., 1995); 1,600 vs. 900 (Slemenda et al., 1997) resulted in greater increase in spinal BMC for higher intake groups.
M - 1,310 F - 1,070	Calcium intakes (mg/d) of: 1,314 vs. 960 (Lloyd et al., 1993) 1,437 vs. 728 (Chan et al., 1995) 1,612 vs. 908 (Johnston et al., 1992) resulted in a mean increase in BMC for all higher intake groups.
M - 1,236 F - 1,026	No data
M/F - 840–950 based on calcium balance	Calcium intakes (mg/d) of 1,572 vs. 810 resulted in reduced vertebral bone loss in premenopausal women (Baran et al., 1990).
M - 995	Calcium intake (mg/d) of > 1,200 resulted in no difference in bone loss in males.
F - 1200[e] as predicted from balance studies	Calcium intake (mg/d) of > 750, 800 and 1,000 showed less bone loss than lower intakes in females (see Table 4-1).
No data;[e] 1,200 mg extrapolated from data in 51–70 year olds	Calcium intake (mg/d) of 1,200 vs. 750 resulted in reduced fracture rate and lower bone loss measured by BMD at various sites (Chapuy et al., 1992; Dawson-Hughes et al., 1997).

estimate of the intake at which a desirable calcium retention would be attained (see text for specific values used for each age group; see Appendix E for equations).

[d] The major outcome evaluated from the clinical trials reviewed was change in BMD at various bone sites or fracture rate in the > 70 year age group.

[e] These estimates were not derived from statistical analysis of calcium intake and retention data to determine desirable calcium intakes due to limitations in the range of calcium intakes that had been studied.

not clear. Significant increases in maternal calcium accretion, bone turnover, and intestinal absorption early in pregnancy, prior to the mineralization of the fetal skeleton, have been observed in kinetic and histomorphometric studies (Heaney and Skillman, 1971; Purdie et al., 1988).

Results from balance and calcium kinetic studies in 15 women conducted during pregnancy demonstrated increased calcium retention well in advance of when most of the mineralization of the fetal skeleton occurs (Heaney and Skillman, 1971). The mean calcium intakes ranged from 920 to 2,020 mg (23 to 50.5 mmol)/day throughout pregnancy. Calcium retention exceeded the demand for fetal growth. A possible explanation for the increased calcium retention in these balance studies is that the mothers were still accreting bone regardless of their pregnancy state; the ages of the mothers ranged from 15 to 28 years.

Urinary calcium excretion increases during pregnancy and is related to the elevated serum $1,25(OH)_2D$ and increased intestinal absorption of calcium (Gertner et al., 1986). This physiologic absorptive hypercalciuria has led some investigators to consider pregnancy a "period of calcium feast rather than famine" (Gertner et al., 1986). Whether dietary calcium modulates the $1,25(OH)_2D$ response to pregnancy is not clear.

Indicator Used to Set the AI

Bone Mineral Mass. Whether significant bone resorption occurs during pregnancy to serve as a mineral supply for fetal skeletal needs is not clear. In a prospective study of six women, lumbar spine BMD decreased between prepregnancy and postpartum measurements but increased to baseline values after weaning (Drinkwater and Chesnut, 1991). Another study reported no change in BMD during pregnancy in the radius (Cross et al., 1995a). However, the radius is more cortical than trabecular bone and may not be sensitive to subtle changes in bone mass.

Dietary calcium intake does not appear to influence changes in maternal bone mass during pregnancy. A study in undernourished pregnant mothers found that supplementation with 300 mg (7.5 mmol)/day or 600 mg (15 mmol)/day of calcium did not increase the metacarpal bone density of the mothers during pregnancy when compared with unsupplemented mothers. However, the bone density (determined from radiographs using an aluminum wedge calibration) of the neonates of supplemented mothers was significantly greater (mean of 77 percent greater averaged over four bone sites)

than neonates of the unsupplemented mothers (Raman et al., 1978). Unfortunately, the baseline calcium intake of the unsupplemented mothers was not provided in this study, so the calcium intake associated with the less well-mineralized fetal bone cannot be determined.

A final piece of evidence that supports no increased need for dietary calcium during pregnancy is the lack of a relationship between the number of previous pregnancies and BMD (Alderman et al., 1986; Koetting and Wardlaw, 1988; Kreiger et al., 1982; Walker et al., 1972; Wasnich et al., 1983) or fracture risk (Johansson et al., 1993). Moreover, some studies support a positive correlation between the number of children born and either radial BMD or total body calcium (Aloia et al., 1983), as well as a reduction in hip fracture risk (Hoffman et al., 1993). It was not stated in these studies whether calcium intake modified the relationship between the number of pregnancies and BMD or fracture risk.

AI Summary for Pregnancy

Taken together, the available data on bone mineral mass during pregnancy and the lack of correlation between the number of pregnancies and BMD or fracture risk provide sufficient information to support the concept that the maternal skeleton is not used as a reserve for fetal calcium needs. Adaptive maternal responses to fetal calcium needs include an enhanced efficiency of absorption, which is modulated through changes in calciotropic hormones. Thus, provided that dietary calcium intake is sufficient for maximizing bone accretion rates in the nonpregnant state, the AI does not have to be increased during pregnancy.

AI for Pregnancy	**14 through 18 years**	**1,300 mg (32.5 mmol)/day**
	19 through 30 years	**1,000 mg (25 mmol)/day**
	31 through 50 years	**1,000 mg (25 mmol)/day**

Based on the 1994 CSFII intake data from 33 pregnant women, as adjusted for day-to-day variation (Nusser et al., 1996), the median intake of calcium for pregnant women is 1,154 mg (28.9 mmol)/day, twenty-fifth percentile of calcium intake is 939 mg (23.5 mmol)/day, and the seventy-fifth percentile of intake is 1,382 mg (34.6 mmol)/day (see Appendix D). Thus, the AI of 1,300 mg (32.5 mmol)/day for pregnant women 14 through 18 years of age is between the median and seventy-fifth percentile of calcium intake and the AI of 1,000 mg (25 mmol)/day for pregnant women 19

through 50 years of age is between the twenty-fifth percentile and median intake of calcium.

Special Considerations

Adolescent Pregnancies. The pregnant adolescent woman, theoretically, could have an increased need for calcium because of her need to support her own bone consolidation as well as that of the fetus. Sowers and coworkers (1985) found in a study of 86 women (20 to 35 years of age) that although the number of pregnancies was not associated with BMD of the distal radius, history of a teenage pregnancy (< 20 years of age) was associated with low BMD. Moreover, a lower incidence of preterm delivery and low birth weight was observed in 94 pregnant adolescents (< 17 years of age) randomized to receive 2,000 mg (50 mmol)/day supplemental calcium or a control (n = 95) (Villar and Repke, 1990). Both groups had a mean baseline calcium intake of 1,200 mg (30 mmol)/day. The results of these studies indicate that pregnant adolescents may benefit from a high calcium intake. However, research is needed to establish the plateau dietary intake at which these benefits may occur.

Lactation

The source of calcium utilized by a lactating woman for milk production (approximately 210 mg [5.3 mmol]/day [IOM, 1991]) could be from higher dietary intake, increased fractional intestinal absorption, reduced renal excretion, or stimulation of bone resorption. Based on studies utilizing biochemical indicators of calcium metabolism in lactating women (see Table 4-6), measures of serum $1,25(OH)_2D$ concentrations offer the most, albeit conflicting, information. If there is an increase in calcium need, one would assume this need could be met by increased serum $1,25(OH)_2D$ leading to enhanced calcium absorption. Although investigators have reported high serum $1,25(OH)_2D$ concentrations in lactating women (Kumar et al., 1979; Specker et al., 1987), the majority of studies have found no difference in serum concentrations between lactating and nonlactating women (Cross et al., 1995b; Hillman et al., 1981; Kalkwarf et al., 1996; Kent et al., 1990; Wilson et al., 1990). Serum $1,25(OH)_2D$ concentrations are increased during pregnancy (Wilson et al., 1990), and mean $1,25(OH)_2D$ concentrations in both lactating and nonlactating postpartum women tend to be high in the early postpartum period. These higher concentrations do not

persist during lactation, but may increase again following the initiation of weaning (Kalkwarf et al., 1996; Specker et al., 1991a).

Consistent with the lack of an increase in serum $1,25(OH)_2D$ concentrations in lactating women, calcium absorption also does not appear to be increased during lactation (Kalkwarf et al., 1996; Kent et al., 1991; Specker et al., 1994), even among women consuming a relatively low intake (750 mg [18.8 mmol]/day of calcium) (Kalkwarf et al., 1996). A randomized trial of calcium supplementation at approximately 1,000 mg (25 mmol)/day for 5 days in lactating women accustomed to low calcium intakes (approximately 300 mg [7.5 mmol]/day) found no difference between calcium supplementation groups in percent fractional intestinal absorption (Fairweather-Tait et al., 1995).

Biochemical markers and kinetic measurements indicate that bone resorption is increased during lactation (Affinito et al., 1996; Dobnig et al., 1995; Kent et al., 1990) and that this increase is independent of calcium intake (Cross et al., 1995b; Sowers et al., 1995a; Specker et al., 1994). Renal conservation of calcium also has been observed during lactation (Kent et al., 1990; Specker et al., 1994), and both the increased mobilization of calcium from bone and decreased urinary calcium excretion are sufficient to provide calcium for milk production.

These adaptive changes in calcium homeostasis are independent of the calcium intake of the mother and appear to be more dependent on return of ovarian function (Kalkwarf et al., 1996; Sowers et al., 1995b). As a woman regains ovarian function or weans her infant, the serum $1,25(OH)_2D$ concentration increases (Kalkwarf et al., 1996; Specker et al., 1991a), intestinal calcium absorption increases (Kalkwarf et al., 1996), renal retention of calcium persists (Kent et al., 1990), and biochemical markers of bone turnover begin to return to normal levels (Kent et al., 1990; Sowers et al., 1995b).

Indicators Used to Set the AI

Bone Mineral Mass and Fracture. The primary source of calcium secreted in human milk appears to be from increased maternal bone resorption that occurs during lactation (Affinito et al., 1996; Dobnig et al., 1995; Kent et al., 1990), and this increase in resorption is independent of calcium intake (Cross et al., 1995b; Sowers et al., 1995a; Specker et al., 1994).

Data from kinetic studies of lactating and nonlactating women consuming a wide range of calcium intakes indicate that the differ-

TABLE 4-6 Biochemical and Absorption Studies in Women During Lactation

Author and Year	Number Lactating	Number Controls	PP[a] Controls	Ca Intake (mg/day)	Effects of Lactation	Comment
Serum 1,25(OH)$_2$D Concentrations						
Greer et al., 1982c	14	0	No	1,005	Increased over 6 months lactation	
Hillman et al., 1981	28	20	Yes	Not stated	Similar during lactation	4–8 weeks pp[a]
Kalkwarf et al., 1996	24	24	Yes	1,308	Similar during lactation	4.6 months pp
	24	24	Yes	1,213	Higher during weaning	9.6 months pp
Kent et al., 1990	40	40	No	Not stated	Similar during lactation Similar at 2 months post-weaning	
Kumar et al., 1979	6	0	No	Not stated	Higher during lactation	
Markestad et al., 1983	8	17	No	Not stated	Similar during lactation	3.5 months pp
Specker et al., 1987	23	23	Yes	486 1,038	Higher during lactation especially on low Ca intake	
Specker et al., 1991a	26	32	Yes	1,400	Similar during lactation Higher during weaning	
Wilson et al., 1990	27	7	No	Not stated	Similar during lactation	18 weeks pp
Intestinal Calcium Absorption						
Fairweather-Tait et al., 1995	60	0	No	283 997	No effect of Ca intake	3 and 12 months pp
Kalkwarf et al., 1996	24	24	Yes	1,308	Similar during lactation	4.6 months pp
	24	24	Yes	1,213	Higher during weaning	9.6 months pp

Kent et al., 1991	31	26	No	Not stated	Similar during lactation	2 weeks pp
Specker et al., 1994	8	6	No	370	Similar during lactation	
				1,870	No effect of Ca intake	8.5 weeks pp
Renal Calcium Excretion						
Cross et al., 1995a	10	0	No	1,068	Urine lower during weaning	Followed 3 months pw
Kent et al., 1990	40	40	No	Not stated	Lower during lactation and weaning	3.8 months pp 2 and 6 months pw[b]
Kent et al., 1991	31	26	No	Not stated	Lower during lactation and weaning	
Specker et al., 1994	8	6	No	370	Lower during lactation	18 weeks pp
				1,870	especially with low Ca intake	
Bone Turnover						
Affinito et al., 1996	18	18	Yes	1,490	Higher during lactation Similar during weaning	followed 12 months pp
Cross et al., 1995b	15	0	No	1,300	Higher during lactation	30 months pp
				2,400	Unaffected by Ca inake	
Dobnig et al., 1995	35	35	No	Not stated	Higher during lactation	6 months pp
Kent et al., 1990	40	40	No	Not stated	Higher during lactation Similar 6 month after weaning	5.6 months pp
Sowers et al., 1995b	65	20	Yes	1,730	Higher during lactation Similar during weaning	followed 18 months pp
Specker et al., 1994	8	6	No	370	Resorption higher	18 weeks pp
				1,870	during lactation	

[a] pp = postpartum.
[b] pw = postweaning.

ence between bone resorption and formation represents a net flow of calcium from bone into the extracellular fluid calcium compartment of approximately 2.72 mg (0.07 mmol)/kg/day (Specker et al., 1994). Approximately 0.68 mg (0.02 mmol)/kg/day is conserved through reduced renal excretion. The net result is 3.4 mg (0.09 mmol)/kg/day of calcium entering the body pool through stimulation of bone resorption and reduced renal excretion, with an estimated loss in milk of 3.08 mg (0.08 mmol)/kg/day.

Results from longitudinal studies of changes in BMD with lactation indicate that the loss of bone is site specific (see Table 4-7). Results regarding changes in the distal radius are inconsistent (Affinito et al., 1996; Chan et al., 1982a; Hayslip et al., 1989; Kalkwarf and Specker, 1995; Prentice et al., 1990), whereas the majority of studies found decreases in the lumbar spine and femoral neck (Affinito et al., 1996; Cross et al., 1995b; Hayslip et al., 1989; Kalkwarf and Specker, 1995; Kent et al., 1990; Lopez et al., 1996; Sowers et al., 1993). The bone loss observed during lactation appears to be regained upon return of ovarian function (Affinito et al., 1996; Cross et al., 1995a; Kalkwarf and Specker, 1995; Kent et al., 1990; Sowers et al., 1993). These findings during weaning are consistent with changes in biochemical indicators of calcium homeostasis and intestinal absorption that are occurring at this time and with the majority of retrospective studies showing no net deleterious effect of prior lactation on bone mass (see discussion below).

Whether dietary calcium influences the changes in bone mass observed during lactation or affects milk calcium concentrations has been addressed in a few studies (summarized in Table 4-8). The results indicate that the loss of bone mass observed during lactation is not different between women on placebo or supplemental calcium intakes (1,000 mg [25 mmol]/day) (Cross et al., 1995b; Kalkwarf et al., 1997; Prentice et al., 1995) and that milk calcium is unaffected by maternal calcium intake (Kalkwarf et al., 1997; Prentice et al., 1995). The changes in bone mass that occur at this time are likely to be more related to the effects of lack of estrogen than to the increased demand of calcium for milk production. Therefore, it does not appear that dietary calcium intakes above that recommended for nonlactating women minimizes the bone loss observed during lactation, nor does it augment the bone gain during weaning.

Epidemiological studies provide additional support for the assumption that the observed lactation-induced bone loss is a normal physiological response and that after weaning this bone loss is replaced. Many studies have found no association between previous

lactation history and BMD (Koetting and Wardlaw, 1988; Walker et al., 1972; Wasnich et al., 1983) or fracture risk and previous lactation history, although there are studies that report either a decreased (Lissner et al., 1991; Wardlaw and Pike, 1986) or increased (Aloia et al., 1983; Feldblum et al., 1992; Hreshchyshyn et al., 1988; Melton et al., 1993b) BMD with history of lactation (see Table 4-9). A longitudinal prospective study of over 9,000 women over the age of 65 found that the risk of hip fracture was not associated with the number of children who were breast-fed (Cummings et al., 1995). Although most studies have found no increase in fracture risk with a history of lactation, Kreiger and coworkers (1982) found that women who later in life had hip fractures lactated for fewer months than did control women without hip fracture.

AI Summary for Lactation

The loss of calcium from the maternal skeleton that occurs during lactation is not prevented by increased dietary calcium, and the calcium lost appears to be regained following weaning. There is no evidence that calcium intake in lactating women should be increased above that of nonlactating women. Thus, the AIs for calcium during lactation are the same AIs for the nonlactating woman of the same age.

AI for Lactation	**14 through 18 years**	**1,300 mg (32.5 mmol)/day**
	19 through 30 years	**1,000 mg (25 mmol)/day**
	31 through 50 years	**1,000 mg (25 mmol)/day**

Utilizing data as adjusted for day-to-day variation (Nusser et al., 1996) from the 16 lactating mothers in the 1994 CSFII sample, the twenty-fifth percentile of intake for calcium is 982 mg (24.6 mmol)/day (see Appendix D), which is close to the AI of 1,000 mg (25 mmol)/day for lactating women ages 19 through 50 years. The median intake is 1,050 mg (26.3 mmol)/day, the ninety-fifth percentile of intake is 1,324 mg (33.1 mmol)/day, which is slightly above the AI of 1,300 mg (32.5 mmol/day) for lactating women 14 through 18 years of age.

Special Considerations

Closely Spaced Pregnancies. Women aged 20 to 40 years, who breastfeed their infants for at least 6 months and become pregnant within 18 months of initiating lactation have BMDs similar to those of lactating women who do not have a subsequent pregnancy in 18

TABLE 4-7 Longitudinal Studies of Changes in BMD with Lactation

	Group												Postpartum					
Author	Lact	Non Lact (pp)[a]	Wean	Non Wean (pp)	Wean Lact	Wean Non Lact	Lact >6 mo	Lact 0–1 mo	Wean Lact >6 mo	Wean Lact 0–1 mo	*N*	Site	1 mo	3 mo	6 mo	12 mo	Calcium Intake (mg/d)	Percent Change
Affinito et al., 1996	✓										18	LS[c]			✓		1,790	−7.5
		✓									18	LS			✓		1,185	0
	✓										18	R			✓		1,790	−5
		✓									18	R					1,185	0
			✓								18	LS				✓	1,144	3
				✓							18	LS				✓	954	0
			✓								18	R				✓	1,144	2.5
				✓							18	R					954	0
Chan et al., 1982a	✓										39	R[b]			✓		unk	none
Cross et al., 1995b	✓										7	LS		✓	✓		2,400	−6.3
	✓										8	LS		✓			1,300	−4.3
		✓									7	LS		✓			2,400	3.0
		✓									8	LS		✓			1,300	1.7
Hayslip et al., 1989	✓									✓	12	LS			✓		1,786	−6.5
		✓									7	LS			✓		1,253	0
	✓										12	R			✓		1,786	0
		✓									7	R			✓		1,253	0

Kalkwarf and Specker, 1995	✓										65	LS		✓		892	−3.9
		✓									48	LS		✓		723	1.5
	✓										65	R		✓		892	−0.6
		✓									48	R		✓		723	−0.5
			✓								40	LS		✓		763	5.5
				✓							43	LS		✓		732	1.8
			✓								40	R		✓		763	−0.9
				✓							43	R		✓		732	0
Lopez et al., 1996	✓										30	LS	✓			1,479	−4.5[f]
		✓									26	LS	✓			536	0
	✓										30	LS		✓		1,479	−4.5
		✓									26	LS		✓		536	0
								✓			30	LS		✓	pw[e]	1,479	0.5
					✓						26	LS		✓	pw	536	0
	✓										30	FN	✓			1,479	−4.0[f]
		✓									26	FN	✓			536	0
	✓										30	FN		✓		1,479	−7.0
		✓									26	FN		✓		536	0
				✓							30	FN		✓	pw	1,479	1.0
					✓						26	FN		✓	pw	536	0
Sowers et al., 1993						✓					64	LS			✓	1,596	4.3
									✓		20	LS			✓	939	1.4
								✓			64	FN[d]			✓	1,596	2.1
									✓		20	FN			✓	939	0.1

[a] pp = postpartum.
[b] R = radius.
[c] LS = lumbar spine.
[d] FN = femoral neck.
[e] pw = postweaning.
[f] Change relative to controls.

TABLE 4-8 Effect of Calcium Supplementation During Lactation on Changes in BMD

	Group							Postpartum			
Author	Lactating	Non Lactating (pp)[a]	Wean	Non Wean (pp)	Calcium (mg/day)	Number	Site	Weeks	3 mo	6 mo	Percent Change in BMD
Cross et al., 1995b	✓				1,300	7	LS		✓		–4.3
	✓				2,400	8	LS		✓		–6.3
			✓		1,300	7	LS		✓		1.7
			✓		2,400	8	LS		✓		3.0
	✓				1,300	7	Rad (ultra)[e]		✓		~1.5
	✓				2,400	8	Rad (ultra)		✓		5.7
			✓		1,300	7	Rad (ultra)		✓		~–5.7
			✓		2,400	8	Rad (ultra)		✓		~–5.7
	✓				1,300	7	TB		✓		0
	✓				2,400	8	TB		✓		0
Kalkwarf et al., 1997	✓				843	42	LS[b]			✓	–4.9
	✓				1,868	45	LS			✓	–4.2
		✓			656	40	LS			✓	0.4
		✓			1,739	41	LS			✓	2.2
			✓		776	38	LS			✓	4.4
			✓		1,684	38	LS			✓	5.9

					✓	679	42	LS		✓	1.6
					✓	1,744	40	LS		✓	2.5
		✓				843	42	Rad(1/3)[c]		✓	−0.1
		✓				1,868	45	Rad(1/3)		✓	−0.3
			✓			656	40	Rad(1/3)		✓	−0.6
			✓			1,739	41	Rad(1/3)		✓	0
				✓		776	38	Rad(1/3)		✓	−0.4
				✓		1,684	38	Rad(1/3)		✓	−0.8
					✓	679	42	Rad(1/3)		✓	−0.1
					✓	1,744	40	Rad(1/3)		✓	−0.2
		✓				843	42	TB[d]		✓	−3.4
		✓				1,868	45	TB		✓	−2.4
			✓			656	40	TB		✓	−1.2
			✓			1,739	41	TB		✓	−1.7
				✓		776	38	TB		✓	0.2
				✓		1,684	38	TB		✓	−0.2
					✓	679	42	TB		✓	−0.2
					✓	1,744	40	TB		✓	0.4
Prentice et al., 1995		✓				283	30	Rad (mid)[f]	13		−1.1
		✓				997	30	Rad (mid)	13		−1.1
		✓				283	30	Rad (mid)	52		0
		✓				997	30	Rad (mid)	52		0

[a] pp = postpartum.
[b] LS = lumbar spine.
[c] Rad(1/3) = one-third radius.
[d] TB = total body.
[e] Rad (ultra) = ultradistal radius.
[f] Rad (mid) = midshaft radius.

TABLE 4-9 Retrospective or Cross-Sectional Studies Concerning Lactation-Induced Bone Loss

Author	Year	N	Site
Alderman et al.	1986	355	Fracture
		562	Controls
Aloia et al.	1983	80	Radius
Cummings et al.	1995	173	Fracture
		137	Controls
Feldblum et al.	1992	352	Lumbar spine
			Radius
Hoffman et al.	1993	174	Fracture
			Controls
Hreshchyshyn et al.	1988	151	Lumbar spine
Kent et al.	1990	80	Radius
Koetting and Wardlaw	1988	28	Hip, Radius
Kreiger et al.	1982	98	Fracture
		884	Controls
Lissner et al.	1991	126	Lumbar spine
Melton et al.	1993b	304	Hip, Radius, Lumbar spine
Walker et al.	1972	102	Metacarpal
Wardlaw and Pike	1986	21	Radius
Wasnich et al.	1983	608	Radius

months (Sowers et al., 1995b). These findings support those from a cross-sectional study that found similar BMD among women with small or large families (Walker et al., 1972). Therefore, it does not appear, from the data available at this time, that closely spaced pregnancies lead to a lower bone mass in these women than in women with pregnancies less closely spaced.

Feeding More Than One Infant. A study in women breast-feeding twins found significantly higher serum PTH and $1,25(OH)_2D$ concentrations compared to women nursing singletons. The authors suggest that these findings reflect an increased mineral need in the mothers (Greer et al., 1984). No studies have been reported in

Major Findings
Women who lactated more than 2 years had similar risk of fracture as women who never lactated.
Higher radius BMC with lactation (45 to 55 years of age and postmenopausal); no effect of total body Ca.
No increased risk of fracture with history of lactation (>65 years of age).
Higher BMD associated with history of lactation in perimenopausal women 40 to 54 years of age.
No association between hip fracture in women >45 years of age and lactation history.
Higher BMD in women 35 to 65 years of age who lactated compared to no lactation.
BMD at ultradistal radius 7% lower in 40 lactating women at 5.6 months pp compared to 40 controls. No difference at distal or midradius; BMD regained 4 to 6 months pw in 19 women studied.
No association between BMD at 26 to 37 years of age and lactation history. Ca intake not associated with bone measurements.
45 to 74 year olds with hip fractures compared to controls. Cases lactated for less months than nontrauma controls (N = 81) and trauma controls (N = 83).
Lower BMC associated with greater months of lactation.
BMD at any site not associated with lactation. Higher BMD of hip associated with long-term lactation (age-stratified random sample of all adult women in Rochester, MN).
No association between radiograph measurements at 30 to 44 years of age and size of families. Ca intake not associated with bone measurements.
Lower BMC in women 30 to 35 years of age in those who had long-term versus short-term lactation.
BMC in postmenopausal women (44 to 80 years of age) not associated with months of lactation.

which calcium supplementation of lactating mothers of more than one infant was evaluated.

Lactating Adolescents. A study in lactating adolescents found that 15 mothers consuming 900 mg (22.5 mmol)/day calcium had a significant decrease in BMC of the distal radius over the first 16 weeks postpartum. No change was observed in 21 mothers who were consuming 1,850 mg (46.3 mmol)/day of calcium (Chan et al., 1982b). Although the results of these studies are intriguing, several concerns about the findings have been expressed, including not finding bone loss in the adult women, a higher rate of bone loss than that seen in any pathological condition, and bone mass mea-

surements greater than 4 SD above normal at baseline in two of the women (Cunningham and Mazess, 1983; Greer and Garn, 1982). Moreover, it is not clear whether the adolescents were randomized to receive intensive counseling and why there were uneven sample sizes in the two groups of lactating adolescents (n = 15 and 21). Due to the small sample sizes and the uncertainties regarding this study, it is not clear whether the calcium AI in lactating adolescents should be higher than the AI of 1,300 mg (32.5 mmol)/day in the nonlactating adolescent.

TOLERABLE UPPER INTAKE LEVELS

Hazard Identification

Calcium is among the most ubiquitous of elements found in the human system. As stated earlier, calcium plays a major role in the metabolism of virtually every cell in the body and interacts with a large number of other nutrients. As a result, disturbances of calcium metabolism give rise to a wide variety of adverse reactions. Disturbances of calcium metabolism, particularly those that are characterized by changes in extracellular ionized calcium concentration, can cause damage in the function and structure of many organs and systems.

Currently, the available data on the adverse effects of excess calcium intake in humans primarily concerns calcium intake from nutrient supplements. Of the many possible adverse effects of excessive calcium intake, the three most widely studied and biologically important are: kidney stone formation (nephrolithiasis), the syndrome of hypercalcemia and renal insufficiency with and without alkalosis (referred to historically as milk-alkali syndrome when associated with a constellation of peptic ulcer treatments), and the interaction of calcium with the absorption of other essential minerals. These are not the only adverse effects associated with excess calcium intake. However, the vast majority of reported effects are related to or result from one of these three conditions.

Nephrolithiasis

Twelve percent of the U.S. population will form a renal stone over their lifetime (Johnson et al., 1979), and it has generally been assumed that nephrolithiasis is, to a large extent, a nutritional disease. Research over the last 40 years has shown that there is a direct relationship between periods of affluence and increased nephroli-

thiasis (Robertson, 1985). A number of dietary factors seem to play a role in determining the incidence of this disease. In addition to being associated with increased calcium intakes, nephrolithiasis appears to be associated with higher intakes of oxalate, protein, and vegetable fiber (Massey et al., 1993). Goldfarb (1994) argued that dietary calcium plays a minor role in nephrolithiasis because only 6 percent of the overall calcium load appears in the urine of normal individuals. Also, the efficiency of calcium absorption is substantially lower when calcium supplements are consumed (Sakhaee et al., 1994).

The issue is made more complex by the association between high sodium intakes and hypercalciuria, since sodium and calcium compete for reabsorption at the same sites in the renal tubules (Goldfarb, 1994). Other minerals, such as phosphorus and magnesium, also are risk factors in stone formation (Pak, 1988). These findings suggest that excess calcium intake may play only a contributing role in the development of nephrolithiasis.

Two recent companion prospective epidemiologic studies in men (Curhan et al., 1993) and women (Curhan et al., 1997) with no history of kidney stones found that intakes of dietary calcium greater than 1,050 mg (26.3 mmol)/day in men and greater than 1,098 mg (27.5 mmol)/day in women were associated with a reduced risk of symptomatic kidney stones. This association for dietary calcium was attenuated when the intake of magnesium and phosphorus were included in the model for women (Curhan et al., 1997). This apparent protective effect of dietary calcium is attributed to the binding by calcium in the intestinal lumen of oxalate, which is a critical component of most kidney stones. In contrast, Curhan et al. (1997) found that after adjustment for age, intake of supplemental calcium was associated with an increased risk for kidney stones. After adjustment for potential confounders, the relative risk among women who took supplemental calcium, compared with women who did not, was 1.2. Calcium supplements may be taken without food, which limits opportunity for the beneficial effect of binding oxalate in the intestine. A similar effect of supplemental calcium was observed in men (Curhan et al., 1993) but failed to reach statistical significance. Neither study controlled for the time that calcium supplements were taken (for example, with or without meals); thus, it is possible that the observed significance of the results in women may be due to different uses of calcium supplements by men and women. Clearly, more carefully controlled studies are needed to determine the strength of the causal association between calcium

intake vis-à-vis the intake of other nutrients and kidney stones in healthy individuals.

The association between calcium intake and urinary calcium excretion is weaker in children than in adults. However, as observed in adults, increased levels of dietary sodium are significantly associated with increased urinary calcium excretion in children (Matkovic et al., 1995; O'Brien et al., 1996).

Hypercalcemia and Renal Insufficiency (Milk-Alkali Syndrome)

The syndrome of hypercalcemia and, consequently, renal insufficiency with or without metabolic alkalosis is associated with severe clinical and metabolic derangements affecting virtually every organ system (Orwoll, 1982). Renal failure may be reversible but may also be progressive if the syndrome is unrelieved. Progressive renal failure may result in the deposition of calcium in soft tissues including the kidney (for example, nephrocalcinosis) with a potentially fatal outcome (Junor and Catto, 1976). This syndrome was first termed milk-alkali syndrome (MAS) in the context of the high milk and absorbable antacid intake which derived from the "Sippy diet" regimen for the treatment of peptic ulcer disease. MAS needs to be distinguished from primary hyperparathyroidism, in which primary abnormality of the parathyroid gland results in hypercalcemia, metabolic derangement, and impaired renal calcium resorption. As the treatment of peptic ulcers has changed (for example, systemically absorbed antacids and large quantities of milk are now rarely prescribed), the incidence of this syndrome has decreased (Whiting and Wood, 1997).

A review of the literature revealed 26 reported cases of MAS linked to high calcium intake from supplements and food since 1980 without other causes of underlying renal disease (Table 4-10). These reports described what appears to be the same syndrome at supplemental calcium intakes of 1.5 to 16.5 g (37.5 to 412.5 mmol)/day for 2 days to 30 years. Estimates of the occurrence of MAS in the North American population may be low since mild cases are often overlooked and the disorder may be confused with a number of other syndromes presenting with hypercalcemia.

No reported cases of MAS in children were found in the literature. This was not unexpected since children have very high rates of bone turnover and calcium utilization relative to adults (Abrams et al., 1992). A single case of severe constipation directly linked to daily calcium supplementation of 1,000 mg (25 mmol) or more has been reported in an 8-year-old boy, but this may represent an idio-

syncratic reaction of calcium ions exerted locally in the intestine or colon (Frithz et al., 1991).

Calcium/Mineral Interactions

Calcium interacts with iron, zinc, magnesium, and phosphorus (Clarkson et al., 1967; Hallberg et al., 1992; Schiller et al., 1989; Spencer et al., 1965). Calcium-mineral interactions are more difficult to quantify than nephrolithiasis and MAS, since in many cases the interaction of calcium with several other nutrients results in changes in the absorption and utilization of each. Thus, it is virtually impossible to determine a dietary level at which calcium intake alone disturbs the absorption or metabolism of other minerals. Nevertheless, calcium clearly inhibits iron absorption in a dose-dependent and dose-saturable fashion (Hallberg et al., 1992). However, the available human data fail to show cases of iron deficiency or even reduced iron stores as a result of calcium intake (Snedeker et al., 1982; Sokoll and Dawson-Hughes, 1992). Similarly, except for a single report of negative zinc balance in the presence of calcium supplementation (Wood and Zheng, 1990), the effects of calcium on zinc absorption have not been shown to be associated with zinc depletion or undernutrition. Neither have interactions of high levels of calcium with magnesium or phosphorus shown evidence of depletion of the affected nutrient (Shils, 1994).

Thus, in the absence of clinically or functionally significant depletion of the affected nutrient, calcium interaction with other minerals represents a potential risk rather than an adverse effect, in the sense that nephrolithiasis or hypercalcemia are adverse effects. Still, the potential for increased risk of mineral depletion in vulnerable populations such as those on very low mineral intakes or the elderly needs to be incorporated into the uncertainty factor in deriving a UL for calcium. Furthermore, because of their potential to increase the risk of mineral depletion in vulnerable populations, calcium-mineral interactions should be the subject of additional studies.

Dose-Response Assessment

Adults: Ages 19 through 70 Years

Data Selection. Based on the discussion of adverse effects of excess calcium intake above, the most appropriate data available for identifying a critical endpoint and a no-observed-adverse-effect level (NOAEL) (or lowest-observed-adverse-effect level [LOAEL]) con-

cern risk of MAS or nephrolithiasis. There are few well-controlled, chronic studies of calcium that show a dose-response relationship. While there are inadequate data on nephrolithiasis to establish a dose-response relationship and to identify a NOAEL (or LOAEL), there are adequate data on MAS that can be used.

Identification of a NOAEL (or LOAEL) and Critical Endpoint. Using MAS as the clinically defined critical endpoint, a LOAEL in the range of 4 to 5 grams (100 to 125 mmol)/day can be identified for adults (Table 4-10). A review of these reports revealed calcium intakes from supplements (and in some cases from dietary sources as well) in the range of 1.5 to 16.5 g (37.5 to 412.5 mmol)/day. A median intake of 4.8 g (120 mmol)/day resulted in documented cases. Since many of these reports included dietary calcium intake as well as intake from supplements, an intake in the range of 5 g (125 mmol)/day represents a LOAEL for total calcium intake (for example, from both supplements and food). A solid figure for a NOAEL is not available, but researchers have observed that daily calcium intakes of 1,500 to 2,400 mg (37.5 to 60 mmol) (including supplements), used to treat or prevent osteoporosis, did not result in hypercalcemic syndromes (Kochersberger et al., 1991; McCarron and Morris, 1985; Riggs et al., 1996; Saunders et al., 1988; Smith et al., 1989; Thys-Jacobs et al., 1989).

Consideration of hypercalciuria may have additional relevance to the derivation of a UL for adults. Hypercalciuria is observed in approximately 50 percent of patients with calcium oxalate/apatite nephrolithiasis and is an important risk factor for nephrolithiasis (Lemann et al., 1991; Whiting and Wood, 1997). Therefore, it is plausible that high calcium intakes associated with hypercalciuria could produce nephrolithiasis. Burtis et al. (1994) reported a significant positive association between both dietary calcium and sodium intake and hypercalciuria in 282 renal stone patients and derived a regression equation to predict the separate effects of dietary calcium and urinary sodium on urinary calcium excretion. Setting urinary sodium excretion at 150 mmol/day and defining hypercalciuria for men as greater than 300 mg (7.5 mmol) of calcium/day excreted (Burtis et al., 1994), the calcium intake that would be associated with hypercalciuria was 1,685 mg (42.1 mmol)/day. For women, for whom hypercalcemia was defined as greater than 250 mg (6.2 mmol)/day excreted, it would be 866 mg (21.6 mmol)/day. The results of these calculations from the Burtis et al. (1994) equation suggest that calcium intakes lower than AI levels derived earlier in this chapter for females could result in hypercalciuria in susceptible individuals.

TABLE 4-10 Case Reports of Milk Alkali Syndrome (single dose/day)[a]

Studies	Ca Intake (g/d)[b]	Duration	Mitigating Factors
Abreo et al., 1993	9.6[c]	>3 mo	None reported
	3.6[c]	>2 y	None reported
	10.8[d]	Not stated	None reported
Brandwein and Sigman, 1994	2.7[c]	2 y, 8 mo	None reported
Bullimore and Miloszewski, 1987	6.5[d]	23 y	Alkali in antacid
Campbell et al., 1994	5[d]	3 mo	None reported
Carroll et al., 1983	4.2[d]	30 y	None reported
	2[c]	5 y	None reported
	3.8[d]	2 mo	Vitamins A and E
	2.8[d]	10 y	$NaHCO_3$, 5 g/d
French et al., 1986	8[c]	2 y	None reported
	4.2[c]	>2 y	Thiazide
Gora et al., 1989	4[c]	2 y	Thiazide
Hart et al., 1982	10.6[d]	Not stated	$NaHCO_3$, 2 g/d
Kallmeyer and Funston, 1983	8[d]	10 y	Alkali in antacid
Kapsner et al., 1986	10[d]	10 mo	None reported
	6.8[d]	7 mo	None reported
	4.8[c]	2 d	10-y history of antacid use
Kleinman et al., 1991	16.5[d]	2 wk	10-y history of antacid use
Lin et al., 1996	1.5[c]	4 wk	None reported
Muldowney and Mazbar, 1996	1.7[c]	13 mo (52 wk)	None reported
Schuman and Jones, 1985	9.8[d]	20 y	None reported
	4.8[d]	6 wk	10-y history of antacid intake
Whiting and Wood, 1997	2.4[c]	>1 y	None reported
Whiting and Wood, 1997	2.3–4.6[c]	>1 y	None reported
Number of Subjects	26		
Mean	5.9	3 y, 8 mo	
Median	4.8	13 mo	
Range	1.5–>16.5	2 d–23 y	

[a] Case reports of patients with renal failure are not included in this table.
[b] Intake estimates provided by Whiting and Wood (1997).
[c] Calcium intake from supplements only.
[d] Calcium intake from supplements and diet.

Although Burtis et al. (1994) identified what could be defined as LOAELs for hypercalciuria, 1,685 mg (42.1 mmol)/day in men and 866 mg (21.6 mmol)/day in women, these values are not considered as appropriate for use as the LOAEL for healthy adults as they were based on patients with renal stones. However, they support for the need for conservative estimates of the Tolerable Upper Intake Level (UL).

Uncertainty Assessment. An uncertainty factor (UF) of 2 is recommended to take into account the potential for increased risk of high calcium intake based on the following: (1) 12 percent of the American population is estimated to have renal stones, (2) hypercalciuria has been shown to occur with intakes as low as 1,700 mg (42.5 mmol)/day in male and 870 mg (21.7 mmol)/day in female patients with renal stones (Burtis et al., 1994), and (3) concern for the potential increased risk of mineral depletion in vulnerable populations due to the interference of calcium on mineral bioavailability, especially iron and zinc.

TABLE 4-11 Case Reports of Milk Alkali Syndrome (multi- and increasing doses)

	Ca Intake (Dose 1) (g/d)	Duration (mo)	Ca Intake (Dose 2) (g/d)	Duration
Beall and Scofield, 1995	1[a]	13	2.4[a]	2 wk
	1	13	4.2	2 wk
	0.3[a]	6	1.8[a]	1 mo
Carroll et al., 1983	2.5	13	3	13 mo
Dorsch, 1986	Not reported	13	2.1[a]	6 mo
Hakim et al., 1979	1[a]	13	2.5[a]	3.5 wk
Malone and Horn, 1971	Not reported	13	3[a]	4.5 wk
Newmark and Nugent, 1993	Not reported	13	8.4[a]	<1 y ("recent")
Schuman and Jones, 1985	Not reported	13	4.6	6 wk
Number of Subjects	9		9	
Mean	1.2	12	3.6	16.7
Median	1	13	3	4.5
Range	0.3–2.5	6–13	1.8–8.4	2–53 wk

[a] Data do not include intake of calcium from dietary sources.

Derivation of the UL. A UL of 2.5 g (62.5 mmol)/day is calculated by dividing a LOAEL of 5 g (125 mmol)/day by the UF of 2. The data summarized in Table 4-11 show that calcium intakes of 0.3 to 2.5 g (7.5 to 62.5 mmol)/day have not been shown to cause MAS and provide supportive evidence for a UL of 2,500 mg (62.5 mmol)/day for adults. The estimated UL for calcium in adults is judged to be conservative. For individuals who are particularly susceptible to high calcium intakes, such as those with hypercalcemia and hyperabsorptive hypercalciuria, this level or below should be protective.

UL for Adults 19 through 70 years 2,500 mg (62.5 mmol)/day

Infants: Ages 0 through 12 Months

The safety of calcium intakes above the levels provided by infant formulas and weaning foods has recently been studied by Dalton et al. (1997). They did not find any effect on iron status from calcium intakes of approximately 1,700 mg (42.5 mmol)/day in infants, which was attained using calcium-fortified infant formula. However, further studies are needed before a UL specific to infants can be established.

UL for Infants 0 through 12 months Not possible to establish for supplementary calcium

Toddlers, Children, and Adolescents: Ages 1 through 18 years

Although the safety of excess calcium intake in children ages 1 through 18 years has not been studied, a UL of 2,500 mg (62.5 mmol)/day is recommended for these life stage groups. Although calcium supplementation in children may appear to pose minimal risk of MAS or hyperabsorptive hypercalciuria, risk of depletion of other minerals associated with high calcium intakes may be greater. With high calcium intake, small children may be especially susceptible to deficiency of iron and zinc (Golden and Golden, 1981; Schlesinger et al., 1992; Simmer et al., 1988). However, no dose-response data exist regarding these interactions in children or the development of adaptation to chronic high calcium intakes. After age 9, rates of calcium absorption and bone formation begin to increase in preparation for pubertal development, but a conservative UL of 2,500 mg (62.5 mmol)/day (from diet and supplements) is recommended for children due to the lack of data.

UL for Children 1 through 18 years 2,500 mg (62.5 mmol)/day

Older Adults: Ages > 70 Years

Several physiologic differences in older adults need to be considered in setting the UL for people over age 70. Because this population is more likely to have achlorhydria (Recker, 1985), absorption of calcium, except when associated with meals, is likely to be somewhat impaired, which would protect these individuals from the adverse effects of high calcium intakes. Furthermore, there is a decline in calcium absorption associated with age that results from changes in function of the intestine (Ebeling et al., 1994). However, the elderly population is also more likely to have marginal zinc status, which theoretically would make them more susceptible to the negative interactions of calcium and zinc (Wood and Zheng, 1990). This matter deserves more study. These effects serve to increase the UF on the one hand and decrease it on the other, with the final result being to use the same UL for older adults as for younger adults.

UL for Older Adults	**> 70 years**	**2,500 mg (62.5 mmol)/day**

Pregnancy and Lactation

The available data were judged to be inadequate for deriving a UL for pregnant and lactating women that is different from the UL for the nonpregnant and nonlactating female.

UL for Pregnancy	**14 through 50 years**	**2,500 mg (62.5 mmol)/day**
UL for Lactation	**14 through 50 years**	**2,500 mg (62.5 mmol)/day**

Special Considerations

Not surprisingly, the ubiquitous nature of calcium results in a population of individuals with a wide range of sensitivities to its toxic effects. Subpopulations known to be particularly susceptible to the toxic effects of calcium include individuals with renal failure, those using thiazide diuretics (Whiting and Wood, 1997), and those with low intakes of minerals that interact with calcium (for example, iron, magnesium, zinc). For the majority of the general population, intakes of calcium from food substantially above the UL are probably safe.

Exposure Assessment

The highest median intake of calcium for any age group found in the 1994 CSFII data, adjusted for day-to-day variation (Nusser et al., 1996), was for boys 14 through 18 years of age with a median intake of 1,094 mg (27.4 mmol)/day and a ninety-fifth percentile intake of 2,039 mg (51 mmol)/day (see Appendix D). Calcium supplements were used by less than 8 percent of young children, 14 percent of men, and 25 percent of women in the United States (Moss et al., 1989). Daily dosages from supplements at the ninety-fifth percentile were relatively small for children (160 mg [4 mmol]), larger for men (624 mg [15.6 mmol]), and largest for women (904 mg [22.6 mmol]) according to Moss et al. (1989).

Risk Characterization

Although the ninety-fifth percentile of daily intake did not exceed the UL for any age group (2,101 mg [52.5 mmol] in males 14 through 18 years old) in the 1994 CSFII, persons with a very high caloric intake, especially if intakes of dairy products are also high, may exceed the UL of 2,500 mg (62.5 mmol)/day.

Even if the ninety-fifth percentile of intake from foods and the most recently available estimate of the ninety-fifth percentile of supplement use (Moss et al., 1989) are added together for teenage boys (1,920 + 928 mg/day) or for teenage girls (1,236 + 1,200 mg/day), total intakes are just at or slightly above the UL. Although users of dietary supplements (of any kind) tend to also have higher intakes of calcium from food than nonusers (Slesinski et al., 1996), it is unlikely that the same person would fall at the upper end of both ranges. Furthermore, the prevalence of usual intakes (from foods plus supplements) above the UL is well below 5 percent, even for age groups with relatively high intakes. Nevertheless, an informal survey of food products in supermarkets in the Washington, D.C. metropolitan area between 1994 and 1996 showed that the number of calcium-fortified products doubled in the 2-year period (Park Y., February, 1997, personal communication). Therefore, it is important to maintain surveillance of the calcium-fortified products in the marketplace and monitor their impact on calcium intake.

RESEARCH RECOMMENDATIONS

Balance studies can be used to determine the amount of calcium needed in the diet to support desirable calcium retention. Such studies need to be expanded in the following ways:

- To the extent possible, balance studies should be augmented with stable or radioactive tracers of calcium to estimate aspects of calcium homeostasis with changes in defined intakes (i.e., fractional absorption, bone calcium balance, and bone turnover rates);
- Adaptations to changes in the amount of dietary calcium should be followed within the same populations for short-term (2 months) to long-term (1 to 2 years) studies. Different experimental approaches will be needed to define the temporal response to changes in dietary calcium. Short-term studies may be conducted in a metabolic unit whereas the longer-term studies will need to be carried out in confined populations (i.e., convalescent home patients) fed prescribed diets; human study cohorts followed carefully for years with frequent, thorough estimates of dietary intakes; or metabolic studies of individuals fed their usual diets who typically consume a wide range of calcium intakes. All studies should include a comprehensive evaluation of biochemical measures of bone mineral content or metabolism. Bone mineral content and density should be evaluated in long-term studies. Good surrogate markers of osteopenia could be used in epidemiological studies.
- Assessment of the effect of ethnicity and osteoporosis phenotype on the relationship between dietary calcium, desirable calcium retention, bone metabolism, and bone mineral content.
- Evaluation of the independent impact of diet, lifestyle (especially physical activity), and hormonal changes on the utilization of dietary calcium for bone deposition and growth in children and adolescents. These studies need to be done in populations for which the usual calcium intakes range from low to above adequate.
- Epidemiological studies of the interrelationships between calcium intake and fracture risk, osteoporosis, prostate cancer, and hypertension must be pursued to determine if calcium intake is an independent determinant of any of these health outcomes. Control of other factors potentially associated as other risk factors for these health problems is essential (for example, fat intake in relation to cancer and cardiovascular disease; weight bearing activity; and dietary components such as salt, protein and caffeine in relation to osteoporosis). Such epidemiological studies need to be conducted in middle-aged as well as older adult men and women.

- More carefully controlled studies are needed to determine the strength of the causal association between calcium intake vis-à-vis the intake of other nutrients and kidney stones in healthy individuals.
- Because of their potential to increase the risk of mineral depletion in vulnerable populations, calcium-mineral interactions should be the subject of additional studies.